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RICHTER-ANSCHÜTZ

THE CHEMISTRY OF THE CARBON COMPOUNDS

Third English Edition

RICHTER-ANSCHÜTZ

THE CHEMISTRY OF THE CARBON COMPOUNDS

Third English edition based on the twelfth German edition

VOLUME ONE

The Aliphatic Series

VOLUME TWO

The Alicyclic Compounds and Natural Products

VOLUME THREE

The Aromatic Compounds

VOLUME FOUR

The Heterocyclic Compounds and Organic Free Radicals

THE CHEMISTRY
OF THE
CARBON COMPOUNDS

BY

VICTOR VON RICHTER

EDITED BY THE LATE PROFESSOR

RICHARD ANSCHÜTZ

VOLUME IV

THE HETEROCYCLIC COMPOUNDS

BY F. REINDEL (*translated by* M. F. DARKEN)

AND

ORGANIC FREE RADICALS

BY LUDWIG ANSCHÜTZ (*translated by* A. J. MEE)

NEWLY TRANSLATED FROM THE TWELFTH GERMAN EDITION

1947
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DEDICATED
TO THE MEMORY
OF
AUGUST KEKULÉ
BY THE EDITORS

PUBLISHER'S NOTE

Volume IV is a literal translation from the twelfth German edition. As pointed out in the Publisher's Note of Volume III, with the outbreak of World War II we were faced with the difficult problem of deciding whether to discontinue publication of the translation and revision of the twelfth German edition with Volume II of this series or to complete the series with a literal translation from the German. The latter procedure was followed for Volume III and approved by the majority of the reviewers despite its shortcomings. We are, therefore, with the fourth volume completing the literal translation of the remaining parts of the German set.

This volume treats of the "Heterocyclic Compounds" (which constituted the third volume of the German original) and of "Free Radicals" (part of Volume II, Part 2, of the German original).

With the publication of Volume IV, the entire twelfth German edition becomes available in an English translation; the user will find in it a concise and comprehensive inventory of the most important organic chemical compounds. As before, an added feature of the present English edition is that, wherever possible, references are given to the original journals and not to *Chemisches Zentralblatt,* and that names of the authors have been added.

We again wish to express our thanks to Dr. A. J. Mee and M. F. Darken for translating, editing, and checking this difficult and complex text, and to Dr. G. Berend for the preparation of the exhaustive index.

ELSEVIER PUBLISHING CO., INC.

May, 1947

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Aliphatic Compounds	I	1928	I	1934
Alicyclic Compounds	II, Part 1	1935	II	1939
Natural Products	II, Part 1	1935	II	1939
Aromatic Compounds	II, Part 2	1935	III	1946
Heterocyclic Compounds	III	1931	IV	1947
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LIST OF ABBREVIATIONS

Acta Acad. Aboensis Math. Phys.	Acta Academiae Aboensis Mathematica et Physica
Acta Schol. Med. Univ. Imp. Kioto	Acta Scholae Medicinalis Universitatis Imperialis in Kioto
Am	Journal of the American Chemical Society
Am. Chem. J	American Chemical Journal
Anal. soc. esp. fis. quim	Anales de la sociedad española de física y química
Angew	Angewandte Chemie
Ann	Annalen der Chemie
Ann. chim	Annales de chimie
Ann. chim. phys	Annales de chimie et de physique
Anz. Akad. Wiss. Krakaw	Anzeiger der Akademie der Wissenschaften in Krakow
Apoth.-Ztg	Apotheker-Zeitung
Arch. Path. Pharm	Archiv für experimentelle Pathologie und Pharmakologie
Arch. Pharm	Archiv der Pharmazie
Atti accad. sci. Torino	Atti della reale accademia delle scienze di Torino
Atti r. accad. Lincei	Atti della reale accademia dei Lincei
Atti cong. naz. chim. pura applicata	Atti del congresso nazionale di chimica pura ed applicata
Beitr. chem. Physiol. Path	Beiträge zur chemischen Physiologie und Pathologie
Ber	Berichte der deutschen chemischen Gesellschaft
Ber. deut. pharm. Ges	Berichte der deutschen pharmazeutischen Gesellschaft
Ber. Verhandl. K. sächs. Ges. Wiss	Berichte über die Verhandlungen der K. sächsischen Gesellschaft der Wissenschaften. Mathematisch-physische Klasse
Biochem. Z	Biochemische Zeitschrift
Brennstoff-Chem	Brennstoff-Chemie
Bull	Bulletin de la société chimique de France
Bull. Chem. Soc. Japan	Bulletin of the Chemical Society of Japan
Bull. soc. chim. Belgique	Bulletin de la société chimique de Belgique
Bull. soc. ind. Mulhouse	Bulletin de la société industrielle de Mulhouse
C	Chemisches Zentralblatt
C.r	Comptes rendus hébdomadaires des séances de l'académie des sciences
C. r. soc. biol	Comptes rendus hébdomadaires des séances de la société de biologie
Chem.-Ztg	Chemiker-Zeitung
Deut. med. Woch	Deutsche medizinische Wochenshrift
Estr. anniaro Soc. chim. Milano	Estratto annario Società chimica di Milano
G. (or Gazz.)	Gazzetta chimica italiana
Helv	Helvetica Chimica Acta
Helv. Physica Acta	Helvetica Physica Acta
Inst. int. Chim. Solvay, Conseil Chim	Institut international de Chimie Solvay, Conseil de Chimie

J.	Journal of the Chemical Society (London)
J. Biol. Chem.	Journal of Biological Chemistry
J. Chem. Phys.	Journal of Chemical Physics
J. chim. phys.	Journal de chimie physique
J. chim. Ukraine	Journal chimique de l'Ukraine
J. Indian Chem. Soc.	Journal, Indian Chemical Society, Calcutta
J. pharm. chim.	Journal de pharmacie et de chimie
J. Pharm. Soc. Japan	Journal of the Pharmeceutical Society of Japan
J. Phys. Chem.	Journal of Physical Chemistry
J pr.	Journal für praktische Chemie (Neue Folge)
J. Russ. Phys.-Chem. Soc.	Journal of the Russian Physical-Chemical Society
Koninkl. Akad. Wettenschappen Amsterdam	Koninklijke Akademie van Wetenschappen te Amsterdam
Med. Klin.	Medizinische Klinik
Mon. sci.	Moniteur scientifique de Quesneville
Mo.	Monatshefte für Chemie
München. med. Wochenschr.	Münchener medizinische Wochenschrift
N.	Naturwissenschaften
Nachr. Ges. Wiss. Göttinger	Nachrichten von der Gesellschaft der Wissenschaften zu Göttinger
Pharm. Weekbl.	Pharmaceutisch Weekblad
Pharm. Zentralhalle	Pharmazeutische Zentralhalle für Deutschland
Proc. Imp. Acad. Tokyo	Proceedings of the Imperial Academy (Tokyo)
Proc. Leeds Phil. Lit. Soc.	Proceedings of the Leeds Philosophical and Literary Society, Scientific Section
Österr. chem.-Z.	Österreichische Chemiker-Zeitung
Proc. Nat. Acad. Sci.	Proceedings of the National Academy of Science
Proc. Roy. Soc.	Proceedings of the Royal Society, London
Quart. J. Indian Chem. Soc.	Quarterly Journal of the Indian Chemical Society
Rec.	Recueil des travaux chimiques des Pays-Bas
Rend. accad. sci. Napoli	Rendiconto dell'accademia delle scienze fisiche e matematiche (Classe della societa reale di Napoli)
Roczniki Chem.	Roczniki Chemji
Sci. Papers Inst. Phys. Chem. Research, Tokyo	Scientific Papers of the Institute of Physical and Chemical Research, Tokyo
Sitz.-ber. heidelberg. Akad. Wiss.	Sitzungsberichte der heidelberger Akademie der Wissenschaften
Sitz.-ber. kgl. preuss. Akad. Wiss.	Sitzungsberichte der königlichen preussischen Akademie der Wissenschaften
Trans. Faraday Soc.	Transactions of the Faraday Society
Z. anal. Chem.	Zeitschrift für analytische Chemie
Z. angew. Chem.	Zeitschrift für angewandte Chemie
Z. anorg. Chem.	Zeitschrift für anorganische Chemie
Z. Farb. Text.-chem.	Zeitschrift für Farben- und Textilchemie
Z. Botan.	Zeitschrift für Botanik
Z. Electrochem.	Zeitsrift für Elektrochemie
Zentr. Physiol.	Zentralblatt für Physiologie
Z. österr. Apoth.-V.	Zeitschrift des allgemeinen österreichischen Apotheker-Vereines
Z. Physik	Zeitschrift für Physik
Z. physikal. Chem.	Zeitschrift für physikalische Chemie
Z. physiol. Chem.	Zeitschrift für physiologische Chemie (Hoppe-Seyler)
Z. Untersuch. Nahr. u. Genussm.	Zeitschrift Untersuchung der Nahrungs und Genussmittel sowie der Gebrauchsgeständе
Z. Ver. deut. Zucker-Ind.	Zeitschrift des Vereins der deutschen Zucker-Industrie

PART I

THE HETEROCYCLIC COMPOUNDS

THE HETEROCYCLIC COMPOUNDS

By F. Reindel

INTRODUCTION

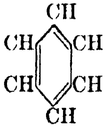
Carbocyclic compounds, described in Volumes II and III of this work, are characterized by having only carbon atoms in their rings. This volume treats of those cyclic compounds whose ring structure is formed of atoms of carbon and of one or more other polyvalent elements. These compounds are termed *heterocyclic compounds* (from ετερος, other), and the atoms other than carbon which occur in their rings are called *hetero atoms*. The most important of the hetero atoms are nitrogen, oxygen, and sulfur. Among the less important hetero atoms are selenium, tellurium, phosphorous, and arsenic. In a few cases iodine (diphenyleneiodinium iodide) and metals join with carbon to form rings. In this classification the salts of dicarboxylic acids with divalent metals are not considered heterocyclic compounds.

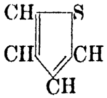
Many heterocyclic compounds which can be obtained from and converted to aliphatic or alicyclic compounds by simple chemical processes, such as hydrolysis or depolymerization, have been described with the parent substances in earlier volumes. Among such compounds are the *polymeric modifications of aldehydes,* such as trioxymethylene and paraldehyde, the *cyclic ethers of glycols and thioglycols,* such as ethylene oxide, diethylene oxide and diethylene disulfide, the *cyclic alkylenimines,* such as tetramethylenimine (pyrrolidine) and diethylenediimine (piperazine), the *cyclic esters of hydroxy and amino acids,* such as lactides, lactones and lactams, and the *cyclic derivatives of dibasic carboxylic acids,* such as anhydrides, imides, alkylene esters and alkylene amides. The description of such compounds logically belongs in the sections dealing with the parent substances.

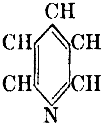
The heterocyclic compounds included in this volume usually possess a stable ring structure which is not readily ruptured. Such a ring structure may be considered as a nucleus, whose derivatives are related to the simple ring structure in the same way as aromatic compounds are related to benzene. The stable heterocyclic rings, like benzene, usually contain several olefinic linkages.

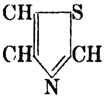
The heterocyclic rings containing five and six members, like the analogous carbon rings, are the most stable and important. The stability of six-membered rings is illustrated by the tendency of *polymerization processes* to form them, as in the polymerization of formaldehyde (Vol. I, p. 233) to trioxymethylene (Vol. I, p. 236), of acetaldehyde (Vol. I, p. 236) to paraldehyde (Vol. I, p. 237) and of cyano compounds to derivatives of a six-membered ring containing three carbon atoms and three nitrogen atoms (Vol. I, p. 520). Five-membered rings also result from polymerization, as in the polymerization of fulminic acid (Vol. I, p. 294), metafulminuric acid, and isocyanilic acid (Vol. I, p. 294). Three- and four-membered rings are usually formed with difficulty and are easily opened. The less familiar seven-membered rings are also unstable. It seems probable, however, that rings larger than this are more stable; the lactone of 16-hydroxy-7-hexadecenoic acid (ambrettolide), which is found in musk seed oil, contains a ring of seventeen members (*Kerschbaum*, Ber. **60**, 903; see Vol. I, p. 454).

Adaptation of *Baeyer's* strain theory to heterocyclic rings is complicated by the different natures of the hetero atoms. However, certain generalizations concerning the relative value of these various atoms or groups in ring structure can be made. Thiophene, with a ring containing four CH-groups and one S-atom, behaves very much like benzene, while thiazole, with a ring containing three CH-groups, one N-atom and one S-atom, resembles pyridine, whose ring is composed of five CH-groups and one N-atom. Therefore, one S-atom in the ring appears to be equivalent to the group —CH=CH—:

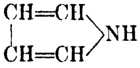

Benzene
b.p. 80.4°

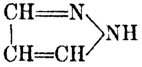

Thiophene
b.p. 84°

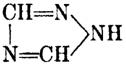

Pyridine
b.p. 115°

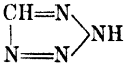

Thiazole
b.p. 117°

The substitution of a CH-group by an N-atom in practically every type of ring structure lessens the stability very little. Pyridine has about the same stability as benzene. By successive replacement of the CH-groups in pyrrole by one, two, and three N-atoms, a series of compounds with similar stability of ring and regular variation of physical properties is obtained:


Pyrrole
liquid


Pyrazole
m.p. 70°

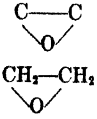

1,2,4-Triazole
m.p. 121°

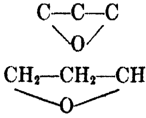

Tetrazole
m.p. 156°

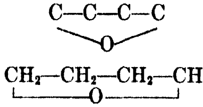
Two systems of classification are possible for heterocyclic ring systems. When classified in homologous series, rings with the same number and kind of hetero atoms are arranged in the order of increasing number of carbon atoms in the ring.

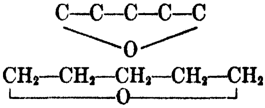
Homologous Series of Heterocyclic Compounds

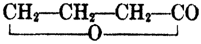
With one O-atom in the ring

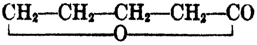

Ethylene oxide
(Vol. I, p. 367)

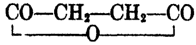

Trimethylene oxide
(Vol. I, p. 368)

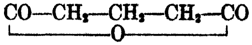

Tetramethylene oxide
(Vol. I, p. 368)


Pentamethylene oxide
(Vol. I, p. 368)

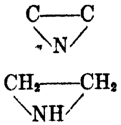

Butyrolactone
(Vol. I, p. 427)

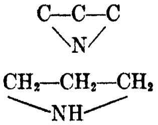

δ-Valerolactone
(Vol. I, p. 427)

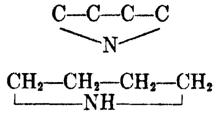

Succinic anhydride
(Vol. I, p. 551)

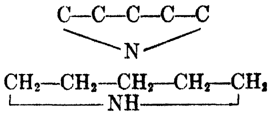

Glutaric anhydride
(Vol. I, p. 557)

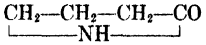
With one N-atom in the ring

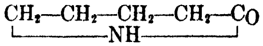

Ethylenimine
(Vol. I, p. 386)

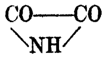

Trimethylenimine
(Vol. I, p. 386)

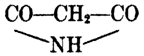

Tetramethylenimine, Pyrrolidine (Vol. I, p. 386)

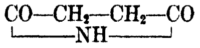

Pentamethylenimine, Piperidine
(Vol. I, p. 386)

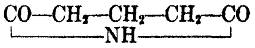

Butyrolactam
(Vol. I, p. 450)

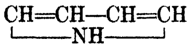

δ-Valerolactam
(Vol. I, p. 451)

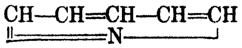

Oxalimide
(Vol. I, p. 539)


Malonimide


Succinimide
(Vol. I, p. 552)


Glutarimide
(Vol. I, p. 557)

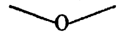

Pyrrole

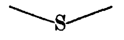

Pyridine

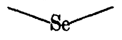
The second system of classification, the one used in this book, arranges the heterocyclic ring systems according to the number of atoms in the ring. This arrangement has the advantage that ring systems with analogous methods of formation and similar stability, or regularly varying stability, are described in sequence. It has the further advantage that the relatively unimportant heterocyclic compounds containing three and four members in their rings are treated in separate sections from the more important ones containing five and more members. Each principal group is subdivided according to the number of hetero atoms in the ring. This system is known as classification in *isologous series* (Vol. I, p. 34). In the following tables its application to the five- and six-membered rings is shown.

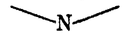
Isologous Series of Heterocyclic Ring Systems

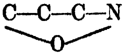
Five-membered heterocyclic rings

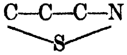

Furans
(γ-lactones, succinic anhydrides)

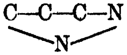

Thiophenes

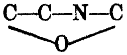

Selenophenes

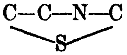

Pyrroles
(γ-lactams, succinimides)

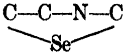

Isoxazoles

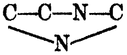

Isothiazoles
(Isobenzothiazoles)

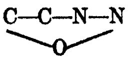

Pyrazoles

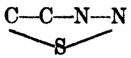

Oxazoles

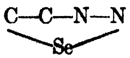

Thiazoles

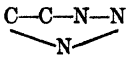

Selenazoles

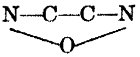

Imidazoles


1,2,3-Oxadiazoles

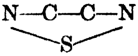

1,2,3-Thiadiazoles


1,2,3-Selenodiazoles

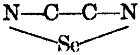

1,2,3-Triazoles



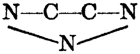
1,2,5-Oxadiazoles
(Furazans)



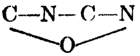
1,2,5-Thiadiazoles
(Piazthioles)



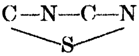
1,2,5-Selenodiazoles
(Piaselenoles)



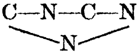
2,1,3-Triazoles



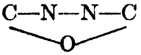
1,2,4-Oxadiazoles
(Azoximes)



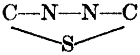
1,2,4-Thiadiazoles
(Azosulfimes)



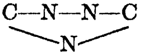
1,2,4-Triazoles



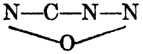
1,3,4-Oxadiazoles



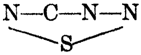
1,3,4-Thiadiazoles



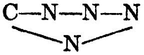
4,1,2-Triazoles



Oxatriazoles
(see v. *Pechmann*,
Ber. **30**, 2874)



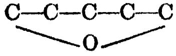
Thiatriazoles



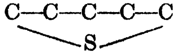
Tetrazoles

Six-membered heterocyclic rings

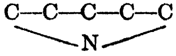
Rings containing more than one O- or S-atom are not included in this table. Ring systems enclosed in brackets have not yet been found.



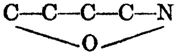
Pyrans



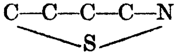
1,4-Thiapyrans



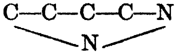
Pyridines



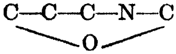
1,2-Oxazines
Orthoxazines



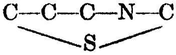
1,2-Thiazines



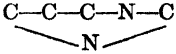
Pyridazines
1,2-Diazines



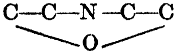
1,3-Oxazines
Metoxazines



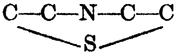
1,3-Thiazines
Metathiazines



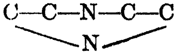
Pyrimidines
1,3-Diazines



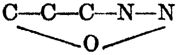
1,4-Oxazines
Paroxazines



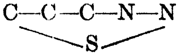
1,4-Thiazines
Parathiazines



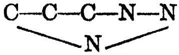
Pyrazines
1,4-Diazines



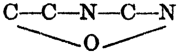
[1,2,3-Oxadiazines]



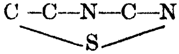
[1,2,3-Thiadiazines]



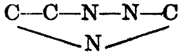
v-Triazines



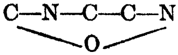
1,2,4-Oxadiazines



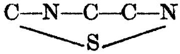
[1,2,4-Thiadiazines]



as-Triazines

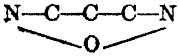


1,2,5-Oxadiazines

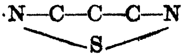


[1,2,5-Thiadiazines]

1,2,5- = 1,2,4- = *as*

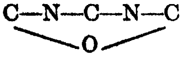


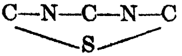
1,2,6-Oxadiazines

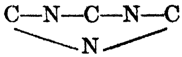


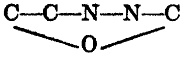
[1,2,6-Thiadiazines]

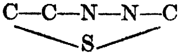
1,2,6- = 1,2,3- = *v*


[1,3,5-Oxadiazines]

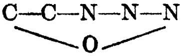

1,3,5-Thiadiazines

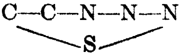

s-Triazines

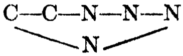

1,3,4-Oxadiazines

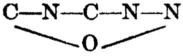

1,3,4-Thiadiazines

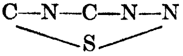
1,3,4- = 1,2,4- = *as*

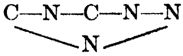

[1,2,3,4-Oxatriazines]

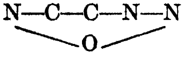

[1,2,3,4-Thiatriazines]

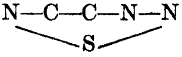

v-Tetrazines


[1,2,3,5-Oxatriazines]

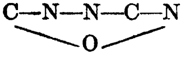

[1,2,3,5-Thiatriazines]

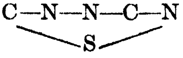

1,2,3,5-Tetrazines

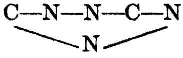

[1,2,3,6-Oxatriazines]

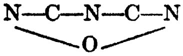

[1,2,3,6-Thiatriazines]

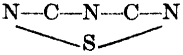
1,2,3,6- = 1,2,3,4- = *v*


[1,2,4,5-Oxatriazines]


[1,2,4,5-Thiatriazines]


s-Tetrazines


[1,2,4,6-Oxatriazines]


[1,2,4,6-Thiatriazines]

1,2,4,6- = 1,2,3,5-

Among the heterocyclic ring systems there are dicyclic and polycyclic *condensed* nuclei which bear the same relation to the simple heterocyclic rings as indene, naphthalene, anthracene, and the like do to benzene. Only the heterocyclic rings containing two neighboring carbon atoms which can also participate in an aromatic ring can form such condensed nuclei. These condensed ring systems combine the properties of carbocyclic and heterocyclic rings. In the absence of a special name, such as indole or quinoline, they are designated by preceding the name of the heterocyclic ring by benzo- or phen-, dibenzo- or diphen-, naphtho-, or the like.

A condensed ring system containing both a heterocyclic and an aromatic ring is almost always formed so that two neighboring carbon atoms are members of both rings. However, compounds in which a heterocyclic ring is joined to a benzene ring in the 1,3-position are known (*Scholtz*, Ber. **35**, 3054; *Autenrieth*, *Beuttel*, Ber. **42**, 4357; *v. Braun*, *Neumann*, Ber. **52**, 2015; *Reindel*, *Schuberth*, Ber. **57**, 369). The rings of bicyclic nuclei formed of two heterocyclic rings share either two neighboring carbon atoms or a carbon atom and an adjoining nitrogen atom. The latter structure is illustrated by a whole series of alkaloids.

Many heterocyclic compounds occur in technical and natural products. The numerous and important plant alkaloids are derivatives of *pyridine* and the hydropyridines. *Pyridine*, *pyrrole*, *thiophene*, *thianaphthene*, and *benzofuran* (coumarone) occur in coal tar, and 2-*furaldehyde* (furfural) and other furan derivatives are found in wood tar. The cleavage of proteins yields many simple and condensed heterocyclic ring systems (proline, hydroxyproline, tryptophan, histidine). Indoles are formed in the putrefaction of albumin.

The physiologically important coloring matters (blood pigments, bile pigments, porphyrins, chlorophyll), which belong to the pyrrole family, illustrate the great significance of heterocyclic compounds in nature. The technical importance of heterocyclic compounds is exemplified by indigo, a derivative of indole; it was obtained from the plant a long time ago, and its synthetic production on a large scale is the result of many advances in chemistry and technology. Many synthetic heterocyclic compounds are prepared technically because of their coloring or pharmaceutical properties. Among these are *thioindigo red* and similar dyes, dyestuffs of the 1,4-*oxazine*, 1,4-*thiazine* and 1,4-*diazine series*, such as *resorufine*, *methylene blue*, *toluylene red*, *safranine* and *indanthrene*, dyestuffs containing the *thiazole grouping*, the important febrifuges of the pyrazole family (*antipyrine* and *pyramidone*, and combinations of these with other pharmacologically active compounds), *piperazine* (hexahydropyrazine), the quinoline derivatives *plasmochin* and *cinchophen* (atophan), and acridine compounds such as *acriflavine* (trypaflavine) and *quinacrine*.

Nomenclature and Numbering of Heterocyclic Ring Systems

The chemical nomenclature in this translation of Volume III of the twelfth edition of *Richter-Anschütz* "Chemie der Kohlenstoffverbindungen" follows the usage of "Chemical Abstracts." The rules for naming and numbering heterocyclic compounds are given in the introduction and appendix of the "Ring Index."* These rules will be stated briefly here:

For many of the ring systems, the generally accepted trivial names, such as furan, pyrrole, and quinoline, are preferred.

For systems with no generally accepted trivial name, a comprehensive system of nomenclature has been devised. These systematic names are intended to give a complete description of the compounds in terms of a limited number of fundamental ring systems, aided by prefixes and position numbers. The authors of the system do not recommend that these names be used exclusively; some heterocyclic compounds are more conveniently considered as acid anhydrides, lactones, or the like.

SIMPLE HETEROCYCLIC RINGS. *Nomenclature:* The systematic names of the simple heterocyclic rings are formed from one component denoting the number and kind of hetero atoms, and another indicating the size of the ring. The former consists of a prefix, such as aza-, oxa-, thia-, diaza-, oxadiaza-, or the like. If more than one kind of hetero atom is present in the ring, the prefixes are combined in the order: O, S, Se, N, P, As.

The size of the ring is expressed by the name ending, such as -ole for five-membered rings, -ine for six-membered rings and -epine for seven-membered rings. For non-nitrogenous rings, the final "e" is dropped from all the endings except -ole.

If the construction of names by this system brings two vowels together, the final vowel of the prefix is dropped, as in azine and oxazole. Its retention in other cases, such as oxadiazole, often marks a departure from the earlier nomenclature.

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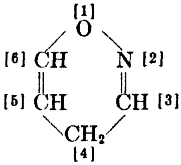
* *Patterson* and *Capell*, The Ring Index. Reinhold, New York, 1940.

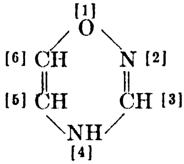
The positions of the hetero atoms and of any "extra" hydrogen atoms (that is, of any group like CH_2 or NH that may be present) are indicated by numbers prefixed to the name. If the "extra" hydrogen atom is on a carbon atom, its position is given after those of the hetero atoms. For example:

1,2,4-Oxazine:



If the "extra" hydrogen atom is on a hetero atom, the position of that hetero atom takes precedence over that of any similar hetero atom. For example:

1,4,2-Oxadiazine:

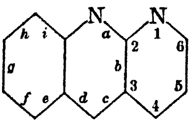


Numbering: The numbering of a ring containing one hetero atom begins on the hetero atom. In rings containing more than one hetero atom, position 1 is assigned according to the order: O, S, Se, N, P, As. The numbering is continued around the ring in the direction that gives the remaining hetero atoms the lowest possible numbers. The term "lowest possible numbers" is taken to mean those that include the lowest individual number or numbers.

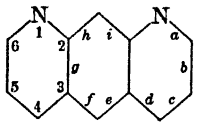
FUSED HETEROCYCLIC SYSTEMS. *Nomenclature:* The systematic names of most heterocyclic polynuclear ring systems are obtained by combining the names of simpler systems which may be thought of as "fused" together to form the system to be named.

One component is chosen as the "parent" form; to its name are attached prefixes denoting the other components. A heterocyclic component is always preferred as parent form before a carbocyclic component, and a nitrogenous component before other heterocyclic components. The largest component with a simple name which conforms to these rules is used for the fundamental part of the name. Thus, "benzoquinoline" is preferred to "quinolinobenzene" and to "naphthopyridine."

The bonds shared by the components of fused systems are indicated by numbers in brackets between the prefix and the fundamental part of the name, and, in more complicated cases, also between prefixes. For this purpose each component is assigned the numbering it would have as a separate system; in order to minimize the use of primes, the sides of the parent compound are lettered *a*, *b*, *c*, etc., in order, beginning with the side 1,2. For example:



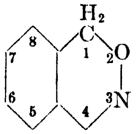
Pyrido[2,3-*b*]quinoline



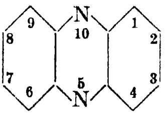
Pyrido[3,2-*g*]quinoline

The reversal of the numbers 2,3 to 3,2 in these names is the means of expressing that the numbers of the fused ring travel with those of the fundamental ring in the first compound, and against them in the second. Wherever possible, unnecessary numbers or letters are omitted; thus, benzo[1,2-*g*]quinoline may be shortened to benzo[*g*]quinoline.

Numbering: Linear polynuclear ring systems containing one or more heterocyclic rings are numbered beginning with that outside ring and in that direction which will give the hetero atoms the lowest possible numbers, in the same order of preference as in mononuclear systems. For example:

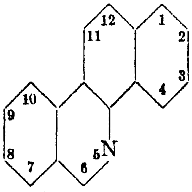


2,3,1-Benzoxazine

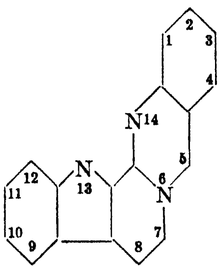


Phenazine

Angular polynuclear ring systems are numbered clockwise from the first free angle of the upper right ring of the formula when it is oriented so that the greatest possible number of rings are in a horizontal row and as many as possible of the remaining rings are above and to the right of the horizontal row:

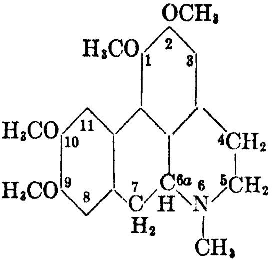


Benzo[*c*]phenanthridine



Indolo[2,3-*c*]quinazo[3,2-*a*]pyridine
(Parent of rutaecarpine)

Interior carbon atoms (common to two or more rings) are designated by adding *a* (or *b*, *c*, etc., in case of a succession of them) to the number of the position just preceding in the clockwise order. If there is a choice of such positions, the highest number is used. For example:



6-Methyl-5,6,6*a*,7-tetrahydro-1,2,9,10-tetramethoxy-4-dibenzo[*de*, *g*]quinoline
(Glaucine)

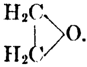
The Ring Index makes a few exceptions from the rules of standard numbering in favor of widely accepted numberings of important parent systems, namely acridine, anthracene, carbazole, cyclopenta[*a*]phenanthrene, phenanthrene, purine, and xanthene, and certain numberings which depend directly on these, such as isocarbazole and isoxanthene.

A. THREE-MEMBERED HETEROCYCLIC COMPOUNDS

The heterocyclic compounds with three-membered rings are generally less stable than the corresponding carbocyclic compounds, and relatively unimportant. The ease with which the rings in such compounds open for the addition of atoms or atomic groups is an indication of ring strain. They are formed only under the most favorable conditions. Several compounds which at first were reported to contain three-membered rings were found on further investigation to be aliphatic compounds or to have double the molecular weight and twice as large a ring.

I. THREE-MEMBERED RINGS WITH ONE HETERO ATOM

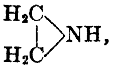
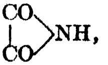
1. WITH ONE OXYGEN ATOM IN THE RING

Ethylene oxide,  The preparation and properties of this compound are described in the section on ethylene glycol in Vol. I. The tendency of this ring to open is so great that ethylene oxide reacts with solutions of metal chlorides to form ethylene chlorohydrin, precipitating the metal as the hydroxide. Substituted ethylene oxides, such as *tetramethylethylene oxide* (Vol. I, p. 368), the *glycidol compounds* (Vol. I, p. 587), and condensed nuclei containing the ethylene oxide ring (such as *tetrahydronaphthalene oxide* and *dioxotetrahydronaphthalene oxide*) behave in the same way.

2. WITH ONE SULFUR ATOM IN THE RING

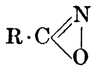
Ethylene sulfide is not known, although its polymers, $(C_2H_4S)_x$ and $(C_2H_4S)_2$ (Vol. I, p. 374), have been prepared. For addition products of sulfur to ethylene and acetylene derivatives, see *Michael*, Ber. **28**, 1635, and *Baumann, Fromm*, Ber. **30**, 110.

3. WITH ONE NITROGEN ATOM IN THE RING

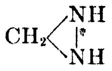
Ethylenimine,  formerly known as vinylamine (Vol. I, p. 199), is prepared by removal of HBr from β-bromoethylamine. **Oxalimide,** obtained from oxamic acid with phosphorus chloride, has been assigned the formula  although the evidence for it is not conclusive (see *de Mouilpied, Rule*, J. **91**, 176).

II. THREE-MEMBERED RINGS WITH TWO HETERO ATOMS

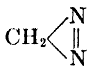
For some time this type of ring was thought to exist in the so-called nitrile oxides (I), hydrazi compounds (II), and aliphatic diazo compounds (III):



I. Nitrile oxides, oxazirines



II. Hydrazi compound, diaziridine



III. Aliphatic diazo compound

Subsequent investigations, especially those of *Angeli* and *Staudinger* (Ber. **44**, 2197, 2203; Helv. **4**, 228), made it evident that all these compounds are very probably aliphatic derivatives, with these formulas:

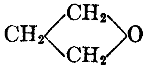
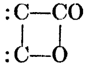
IV. $R{\cdot}C\vdots N{:}O$ V. $CH_2{:}N{\cdot}NH_2$ VI. $CH_2{:}N\vdots N$

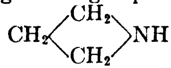
Hydrazi compounds and aliphatic diazo compounds are described in Vol. I, pp. 252–253, and benzonitrile oxide is described in Vol. III, p. 315.

B. FOUR-MEMBERED HETEROCYCLIC COMPOUNDS

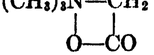
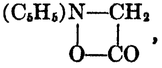
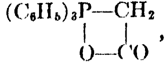
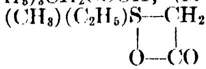
Heterocyclic compounds with four members in their rings are of little importance and will be treated briefly.

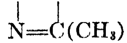
I. FOUR-MEMBERED RINGS WITH ONE HETERO ATOM

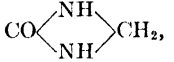
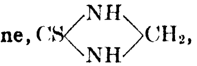
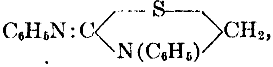
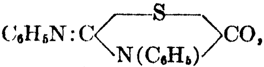
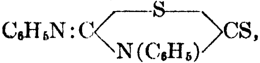
The homologue of ethylene oxide is **trimethylene oxide,** *oxetane,*  (Vol. I, p. 368), of which little is known. The inner anhydrides of β-hydroxycarboxylic acids, or β-lactones, of the formula  (Vol. I, pp. 422, 615, and Vol. III, p. 418) also belong in this group.

Trimethylenimine, *azetidine,*  (Vol. I, p. 386), is prepared, together with 3-methylpyridine, by heating trimethylenediamine; see *Kohn, Morgenstern,* Mo. **28,** 479.

II. FOUR-MEMBERED RINGS WITH TWO HETERO ATOMS

1. Of the heterocyclic compounds whose four-membered rings contain two hetero atoms adjacent to one another, the most important are the cyclic ammonium salts, or **betaines** (Vol. I, pp. 380, 442). All carboxylic acids with a group similar to ammonium hydroxide in the α-position form betaines. **Betaine,**  , is prepared from trimethylglycine chloride, $ClN(CH_3)_3{\cdot}$-$CH_2{\cdot}COOH$, **pyridinium betaine,**  , from 1-carboxymethylpyridinium chloride, $ClN(C_5H_5)CH_2COOH$, **triphenylphosphonium betaine,**  $\begin{array}{l}(C_6H_5)_3P{-}CH_2\\ \quad\;\; | \quad\;\; |\\ \quad\;\; O{-}CO\end{array}$, from carboxymethyltriphenylphosphonium chloride, $ClP(C_6H_5)_3CH_2COOH$, (*Michaelis, Gimborn,* Ber. 27, 273), and **methylethylthetin,**  $\begin{array}{l}(CH_3)(C_2H_5)S{-}CH_2\\ \qquad\qquad\;\; | \quad\;\; |\\ \qquad\qquad\;\; O{-}CO\end{array}$, from the reaction product of methyl ethyl sulfide with bromoacetic acid, $BrS(CH_3)(C_2H_5)CH_2COOH$, (Vol. I, p. 430).

Four-membered rings with two adjacent nitrogen atoms occur in **dimethylaziethane,**  $\begin{array}{l}N{=}C(CH_3)\\ | \quad\;\; |\\ N{=}C(CH_3)\end{array}$, (Vol. I, p. 408), which is prepared from equimolecular quantities of hydrazine hydrate and biacetyl, and probably also in hydrazulmine and azulmic acid (Vol. I, p. 541), formed from ammonia and cyanogen.

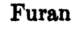
2. Rings with alternate carbon and hetero atoms occur in the cyclic alkylidene-, carbonyl-, and thiocarbonylureas, thioureas and pseudothioureas. **Methyleneurea, 2-uretidone,** , (Vol. I, p. 497), and **methylenethiourea, 2-thiouretidone,** , are formed from urea and thiourea with chloromethanol (*Hemmelmayr,* Mo. 12, 90). **Ethyleneurea, 2-imidazolidone,** and **ethylenethiourea, 2-thioimidazolidone,** are prepared in the same way with acetaldehyde; the 2-anil of **3-phenyl-1,3-thiazetidine, methylenediphenylpseudothiourea,** , is prepared from diphenylthiourea and CH_2I_2 and the 4-oxo derivative, **carbonylthiocarbanilide,** , m.p. 87°, from diphenylthiourea and $COCl_2$, and also by desulfurization of the 4-thio analogue, **thiocarbonylthiocarbanilide,** , m.p. 79°, produced by the action of $CSCl_2$ on diphenylthiourea (*Freund, Wolf,* Ber. 25, 1459).

C. FIVE-MEMBERED HETEROCYCLIC COMPOUNDS

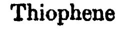
I. FIVE-MEMBERED RINGS WITH ONE HETERO ATOM

FURAN, THIOPHENE (SELENOPHENE), PYRROLE

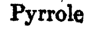
Compounds of the furan, thiophene, and pyrrole groups, which are closely related to one another in methods of formation and chemical behavior, have a basic ring structure consisting of a chain of four CH-groups closed to a ring by O, S, or NH:



Furan



Thiophene

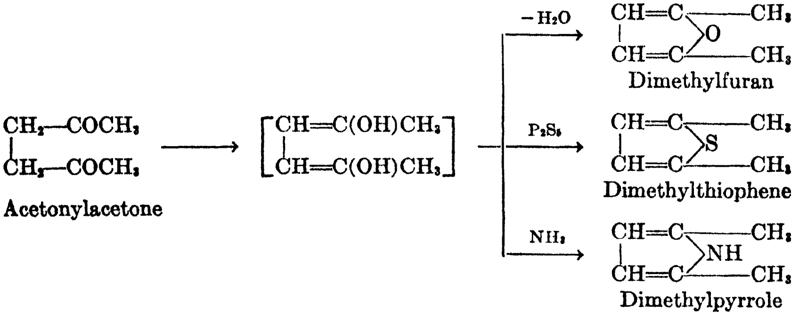


Pyrrole

The parent compounds and their numerous derivatives, especially the thiophenes, show a great similarity to benzene and its derivatives. Many reactions are common to the two types of compounds.

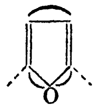
Blue-violet and violet-red dyes are formed by the action of isatin and phenanthraquinone with sulfuric acid on furan, pyrrole, and thiophene compounds.

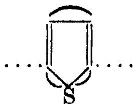
The formation of furan, thiophene, and pyrrole derivatives from γ-diketones is mentioned in connection with the latter in the first volume (Vol. I, p. 404). γ-Diketones yield furans by elimination of water, thiophenes by reaction with phosphorus pentasulfide, and pyrroles by reaction with ammonia or primary amines:

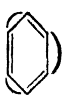


In these reactions the γ-diketones behave as γ-dialkenyl glycols; furans, thiophenes, and pyrroles may be considered as the cyclic anhydrides, sulfides and imines of such glycols. Furans, thiophenes, and pyrroles are also obtained by distillation of mucic and isosaccharic acids, alone or with barium sulfide, or by distillation of the ammonium salts of these acids.

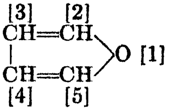
The syntheses described above are in accord with the accepted structural formulas for these compounds. Their peculiar aromatic character is explainable by the assumption, based on an adaptation of Thiele's theory of the structure of the benzene nucleus, "that in these five-membered rings the sulfur, nitrogen, or oxygen atom can partake to some extent in a double bond by the activity of its next higher valency" (*Ciamician*, Ber. **37**, 4254; Gazz. **35**, II, 384). This concept is also implied in the formulas which *Steinkopf* proposes for the ring systems (*Steinkopf*, *Otto*, Ann. **424** 61; *Steinkopf*, Ann. **430**, 78):


Furan

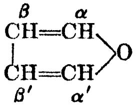

Thiophene


Benzene (Thiele)

To distinguish among the possible isomeric derivatives of furan, thiophene and pyrrole, positions in the ring are designated by numbers, which replace the symbols used in the older literature:



or



Positions 2 and 5 are equivalent, and also positions 3 and 4. The former are the α-positions, and the latter, the β-positions. There are two possible monosubstituted isomers: 2(5)- and 3(4)-. In the disubstituted derivatives, four isomers are possible: 2,5(α,α′)-, 2,3(α,β)-, 2,4(α,β′)-, and 3,4(β,β′)-.

1. FURAN GROUP

This ring system was termed furan (formerly furfuran) because one of its important derivatives is obtained from bran (Latin *furfur*) by heating with hydrochloric acid.

Furan, C_4H_4O, b.p. 32°, was first prepared by distillation of barium pyromucate (p. 20) (*Limpricht*, 1870). It is present in the distillation products of pine wood. It is a liquid, insoluble in water, and has an odor like chloroform. Furan is reduced by passing its vapor mixed with hydrogen over finely divided nickel at 170°; the product is tetrahydrofuran [*Bourguignon*, Bull.soc.chim.Belgique **22** (1908), 87]. With isatin and phenanthraquinone it forms dyes. It reacts violently with hydrochloric acid and forms a black polymerization product. A pine shaving moistened with hydrochloric acid is colored green by furan vapor. Hydrochloric acid in methyl alcohol converts furan to the tetramethyl acetal of succinaldehyde [*Harries*, Chem.-Ztg. **24** (1900), 857]. Furan reacts with an aqueous solution of mercury acetate to form the tetraacetate of tetrahydroxymercurifuran, $C_4O(HgC_2H_3O_2)_4$, dec. 228° (*Cuisa*, *Grillo*, Gazz. **57**, 323). Its behavior in this reaction is analogous to that of thiophene and pyrrole. Spectra of the furans: *v. Auwers*, Ann. **422**, 133.

2-Methylfuran, b.p. 42°, is identical with *sylvan*, which is found in pine tar, with other furan derivatives, and in the creosote from beechwood tar. When the ring is opened with hydrochloric acid, levulinaldehyde, $CH_3COCH_2CH_2CHO$, is formed (*Harries*, Ber. **31**, 37). **2,5-Dimethylfuran,** b.p. 94°, is prepared by decarboxylation of 2,5-dimethylfuran-3,4-dicarboxylic acid (p. 21) by distillation, and by the ring closure of acetonylacetone with dehydrating agents (p. 15). Hydrochloric acid at 170° reconverts it to acetonylacetone.

5-Phenyl-2-methylfuran, m.p. 42°, b.p. 235–240°, is prepared from acetophenoneacetone (*Paal*, Ber. **17**, 915, 2759). Sodium and alcohol reduce it to a tetrahydro compound. **2,5-Diphenylfuran,** m.p. 91°, from diphenacyl (*Perkin*, *Schlösser*, J. **57**, 944; *Engler*, *Dengler*, Ber. **26**, 1447). **2,3,5-Triphenylfuran,** m.p. 93°, from desylacetophenone (*Japp*, *Klingemann*, Ber. **21**, 2933; *Smith*, Ber. **26**, 61). **Tetraphenylfuran,** *lepidene*, m.p. 175°, is formed, together with benzil, when benzoin is heated with hydrochloric acid at 130° (*Japp*, *Klingemann*, Ber. **22**, 2880).

s-Difurylethylene, $C_4H_3O\cdot CH{:}CH\cdot C_4H_3O$, m.p. 101°, analogous to stilbene, is prepared by heating polymeric thiofurfural (*Baumann*, *Fromm*, Ber. **24**, 3591).

Furfuryl alcohol, 2-furanmethanol, $C_4H_3O(CH_2\cdot OH)$, colorless oil, b.p. 171°, b.p. 69° (10 mm.), very soluble in water, resinifies quickly in aqueous and in acid solution. A pine shaving moistened with hydrochloric acid is colored blue-green. It is prepared by the reduction of 2-furaldehyde with sodium amalgam and acetic acid, or catalytically with platinum oxide (*Kaufmann*, *Adams*, Am. **45**, 3029) or biologically with yeast (*Lintner*, Z.physiol.Chem. **72**, 450; **88**, 109). Both furfuryl alcohol and 2-furoic acid are produced by the action of sodium hydroxide on 2-furaldehyde:

$$2C_4H_3O\cdot CHO + H_2O = C_4H_3O\cdot CH_2(OH) + C_4H_3O\cdot COOH.$$

Furfuryl alcohol is present in considerable quantities in oil from roasted coffee. **Diphenylcarbamic acid ester,** $C_4H_3O[CH_2OCON(C_6H_5)_2]$, m.p. 98° (*Erdmann*, Ber. **35**, 1846, 1855). **Methyl ether,** $(C_4H_3O)\cdot CH_2\cdot O\cdot CH_3$, b.p. 134–134° (*v. Wissell*, *Tollens*, Ann. **272**, 291). Furfuryl alcohol is opened by hydrochloric acid in methyl alcohol to the dimethyl acetal of δ-methoxylevulinaldehyde, which is converted to levulinic acid by boiling with aqueous hydrochloric acid (*Pummerer*, *Gump*, Ber. **56**, 999; Vol. I, p. 477).

α-Propylfurfuryl alcohol, $(C_4H_3O)CH(OH)\cdot C_3H_7$, b.p. 93° (12 mm.), is prepared from 2-furaldehyde and propylmagnesium bromide (*Jolkver*, Rec. **28**, 439); 2-furoic acid (p. 20) and dehydromucic acid (p. 20) react with alkylmagnesium halides to form tertiary 2-furanmethanols, $(C_4H_3O)C(OH)R_2$, and 2,5-furandimethanols, $(C_4H_2O)[C(OH)R_2]_2$ (*Hale, McNally, Pater*, Am.Chem.J. **35**, 68).

Halogen-, Nitro- and Aminofurans

Bromofuran can be obtained from brominated 2-furoic acid, and also directly by bromination of furan; with excess bromine it forms addition products. **Diiodofuran**, m.p. 47°, from potassium dehydro-2-furoate with iodine at 100° (*Hill*, Am.Chem.J. **25**, (1901), 439). **Tetraiodofuran**, m.p. 165° (*Cuisa, Grillo*, Gazz. **57**, 323).

3(?)-**Nitrofuran**, m.p. 28°, volatile with steam, is prepared by the nitration of furan with fuming nitric acid in acetic anhydride; an aldehyde (nitrosuccinaldehyde ?) is formed as an intermediate product (*Marquis*, C.r. **134**, 776). A **dinitrofuran**, m.p. 101°, results from nitration of nitrofuran or nitro-2-furoic acid.

2-Aminofuran is obtained in the form of its urethans $C_4H_3O[2]NH{\cdot}COOR$ by boiling furoic acid azide (p. 20) with alcohols; 3-**aminofuran** is obtained in the form of its acetyl derivative, m.p. 112°, by decarboxylation of acetamino-2-furoic acid. The free amines cannot be prepared from these derivatives because NH_3 is split off during saponification (*Leimbach*, J.pr. **65**, 38; *Marquis*, C.r. **136**, 1454).

2-Furanmethylamine, $(C_4H_3O)CH_2NH_2$, b.p. 146°, is prepared by reduction of furonitrile (p. 20) and of the phenylhydrazone of 2-furaldehyde. **2-Furanethylamine**, b.p. 159°, from β-2-furanpropionic acid by the Curtius reaction (*Windaus, Dalmer*, Ber. **53**, 2304).

Aldehydes

FURFURAL, 2-furaldehyde, $C_4H_3O{\cdot}CHO$, m.p. —38.7° (*Timmermans*, Bull.soc.chim.Belgique **31**, 389), b.p. 162°, $d^{13.5}$ 1.163, is prepared by distillation of bran (*furfur*) (*Fownes*, 1849), sugars, especially the pentoses (*Döbereiner*, 1831), or wood with dilute sulfuric acid. It can be detected even in minute amount by the red coloration given with aniline or xylidine (*Schiff*, Ber. **20**, 541; see also p. 19).

Furfural is produced quantitatively by the distillation of pentoses, such as arabinose, with hydrochloric acid. Its condensation product with phloroglucinol is used for the quantitative estimation of the aldehyde. This is the basis for various analytical methods for the estimation of pentoses and pentosans [Vol. I, p. 672; *Steinberger*, Pharm.Weekblad **55**, 782; *Gierisch*, Cellulosechemie **6** (1925), 61]. Glucuronic acid and galacturonic acid (*Dore*, Am. **48**, 232) decompose when heated with hydrochloric acid into furfural, water, and carbon dioxide (*Mann, Tollens*, Ann. **290**, 155).

Furfural is a colorless liquid with an aromatic odor, which turns brown on exposure to air. It is moderately soluble in water and very soluble in alcohol. It has ~~all the~~ properties of an aromatic aldehyde: it combines with bisulfites, it is reduced by sodium amalgam to furfuryl alcohol, it is oxidized by silver oxide to 2-furoic acid, ~~it is converted~~ by potassium hydroxide to the alcohol and the acid; and it reacts with alcoholic KCN solution to form furoin (page 18) and with ammonia ~~to~~ form hydrofuramide (N,N′-di-2-furfurylidene-2-furfurylidenediamine), which corresponds to hydrobenzamide of the benzene series. Hydrogen peroxide or permonosulfuric acid oxidizes it to hydroxyfurfural, $C_4H_2O(OH)$-(CHO), which gives characteristic color reactions with phenols (*Cross, Bevan, Briggs*, Ber. **33**, 3132). Furfural is eliminated from animal organisms as *N-2-furoylglycine, pyromycuric acid*, $C_4H_3O{\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}COOH$, m.p. 165°; in this also it is analogous to benzaldehyde.

Furfuraldoxime, m.p. (α) 75°, (β) 91° (*Brady, Goldstein*, J. **1927**, 1959). **Phenylhydrazone**, m.p. 96°. **Acetal**, $C_4H_3O{\cdot}CH(OC_2H_5)_2$, b.p. 187–190° (*Claisen* Ber. **29**, 1008).

Furfural manifests *all the condensation reactions of benzaldehyde.* (*1*) With dimethylaniline it forms a green dyestuff, corresponding to malachite green (Vol. III, p. 532) (*Fischer*, Ann. **206**, 141; *Fischer*, *Grahl*, J.pr. **100**, 159). (*2*) It condenses with aliphatic aldehydes (compare *Lindauer*, Mo. **21**, 72) and ketones; the products are furaldehydes and ketones unsaturated in the side-chain. The reaction takes place readily in warm dilute sodium hydroxide solution (*Schmidt*, Ber. **13**, 2342). With acetaldehyde **β-2-furanacrolein**, $C_4H_3O\cdot CH:CH\cdot CHO$, m.p. 51°, is obtained, with acetone, **furfurylideneacetone**, $C_4H_3O\cdot CH:CH\cdot CO\cdot CH_3$, and with acetophenone, **furfurylidenemono-** and **diacetophenone** and **difurfurylidenetriacetophenone** (*Kostanecki*, *Podrajansky*, Ber. **29**, 2248). (*3*) As benzoin (Vol. III, p. 564) is formed from benzaldehyde, so furfural is converted by potassium cyanide to **furoin:**

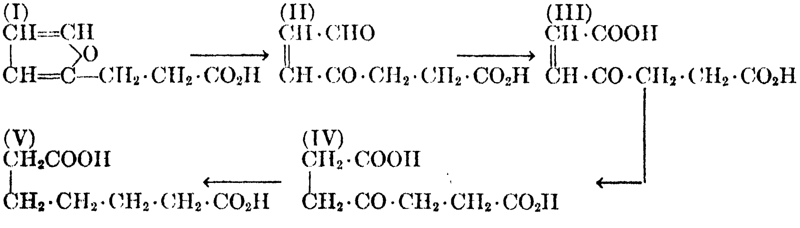
$$2C_4H_3O\cdot CHO = C_4H_3O\cdot CH(OH)\cdot CO\cdot C_4H_3O$$

m.p. 135°. In alkaline solution furoin is oxidized by the oxygen of the air to **furil**, *di-2-furylglyoxal*, $(C_4H_3O)CO\cdot CO(C_4H_3O)$, m.p. 164° (α-dioxime, m.p. 168°, with dec.). Like its prototype benzil (Vol. III, p. 565), furil is reduced by tin and hydrochloric acid to **desoxyfuroin**, $(C_4H_3O)CH_2\cdot CO(C_4H_3O)$. Warm potassium hydroxide converts furil to **furilic acid**, *di-2-furylglycolic acid*, $(C_4H_3O)_2C(OH)\cdot COOH$, analogous to benzilic acid (Vol. III, p. 556).

(*4*) Furfural condenses with the anhydrides and sodium salts of fatty acids on heating (*cf.* the Perkin reaction, Vol. III, p. 268) to give acids of furan with unsaturated side-chains. Furfural with acetic anhydride and sodium acetate forms **β-2-furanacrylic acid**:

$$C_4H_3O\cdot CHO + CH_3\cdot COONa = C_4H_3O\cdot CH:CH\cdot COONa + H_2O$$

β-2-Furanacrylic acid, $C_7H_6O_3$, m.p. 141°, is also obtained from *2-furfurylidenemalonic acid*, the condensation product of furfural and malonic ester [*Dutt*, Quart.J.IndianChem.Soc. **1**, (1925), 297]. Like cinnamic acid, β-2-furanacrylic acid exists in *two stereoisomeric modifications* (*Liebermann*, Ber. **28**, 129). On heating in hydrochloric acid it is opened to acetonediacetic acid (Vol. I, p. 625). Sodium amalgam reduces it to **β-2-furanpropionic acid** (I), $C_4H_3O\cdot CH_2\cdot CH_2\cdot COOH$, m.p. 51°, which is converted by bromine water to *furonaldehyde* (II), which can be reduced stepwise to furonic acid (III), hydrofuronic acid (acetonediacetic acid) (IV), and pimelic acid (V):

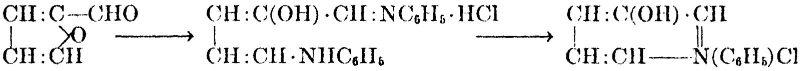


This conversion of furfural to pimelic acid is proof that the aldehyde group is in the 2-position. For other reactions of this type, see *Kehrer*, *Igler*, Ber. **32**, 1176.

α-2-**Furfurylidenebutyric acid**, *furylangelic acid*, $C_4H_3O\cdot CH:C\cdot(CH_2\cdot CH_3)\cdot COOH$, m.p. 88° (ozonide splitting: *Carter*, Am. **50**, 2299) results from the condensation of furfural with butyric acid; it is reduced by sodium amalgam to α-**furfurylbutyric acid**, *furylvaleric acid*. Furfuryl condenses with levulinic acid to δ- or **β-furfurylidenelevulinic acid**, $C_4H_3O\cdot CH:CH\cdot CO\cdot CH_2\cdot CH_2\cdot COOH$, or $C_4H_3O\cdot CH:C(COCH_3)\cdot CH_2\cdot COOH$; the former is formed in an acid medium and the latter in an alkaline one. The latter acid is easily converted to **6-acetyl-4-hydroxybenzofuran** (p. 52). Furfural and succinic acid form various condensation products, according to the conditions of the reaction: **2-furfurylidenesuccinic acid**, $(C_4H_3O)CH:C(CO_2H)\cdot CH_2CO_2H$, *s*-**di-2-furfurylidenesuccinic acid**, $(C_4H_3O)CH:C(CO_2H)\cdot C(CO_2H):CH(C_4H_3O)$, and **α,β-di-2-furfurylidenepropionic acid**, $(C_4H_3O)CH:CH\cdot C(CO_2H):CH(C_4H_3O)$ (*Fichter*, *Scheuermann*, Ber. **34**, 1626; *Titherly, Spencer*, J. **85**, 183). A yellow condensation product is obtained from furfural and 1,3-dimethylbarbituric acid, m.p. 195° [*Akabori*, Proc.Imp. Acad.Tokio **3** (1927), 342].

(*5*) Furfural reacts with aqueous ammonia to form **hydrofuramide**, N,N′-di-2-furfurylidene-2-furfurylidenediamine, $(C_5H_4O)_3N_2$, m.p. 117°. This compound, which is analogous to hydrobenzamide (Vol. III, p. 272), is decomposed into the aldehyde and ammonia by boiling in water; boiling potassium hydroxide solution rearranges it to the isomeric furfurin, m.p. 116° (*cf.* glyoxalines).

(*6*) Primary aromatic amines condense with furfural to form furfurylideneanilines, but amine salts (*Schiff*, Ann. **201**, 355; **239**, 374) attack the furan ring, forming highly colored arylamine derivatives of β-hydroxyglutaconaldehyde, whose hydrochlorides, on boiling with alcohol, split off one molecule of arylamine and condense to colorless N-aryl-β-hydroxypyridinium salts (*Dieckmann, Beck*, Ber. **38**, 4122):



Furfural gives color reactions with 2-naphthol and concentrated sulfuric acid (blue) [*Thomas, Berariu*, C.r. soc.biol. **91** (1924), 1470], and with orcin in the presence of hydrochloric acid (blue, soluble in amyl alcohol) (*Fleury, Poirot*, J.pharm.chim. [7] **26**, 87).

5-Methylfurfural, $C_4H_2(CH_3)O \cdot CHO$, b.p. 184–186°, occurs together with furfural in wood oil (*Hill*, Ber. **22**, 608) and in clove oil (*Masson*, C.r. **149**, 795), and is present in the oil obtained by distillation of varec with sulfuric acid. It is obtained by distillation of rhamnose (Vol. I, p. 675) with sulfuric acid, just as furfural is obtained from arabinose (*Maquenne*, C.r. **109**, 603).

5-Hydroxymethylfurfural, $(C_4H_2O)(CH_2OH)CHO$, m.p. 35°, b.p. 70° (0.002 mm.) (formula: *van Ekenstein, Blanksma*, Ber. **43**, 2355), is produced in the dry distillation of cellulose and by heating hexoses with aqueous oxalic acid under pressure [*Düll*, Chem.-Ztg. **19** (1895), 216; *Kiermayer*, *ibid.* **19** (1895), 1003; *Middendorp*, Rec. **38**, 1]. It is decomposed by hydrochloric acid into formic acid and levulinic acid. Phenylhydrazone: m.p. 141°. Semicarbazone: m.p. 194°. It undergoes several characteristic color and condensation reactions. Condensation product with 1,3-dimethylbarbituric acid: yellow leaflets, m.p. 182° [*Akabori*, Proc.Imp.Acad.Tokyo **3** (1927), 342]. Color reaction with barbituric acid and aniline: sensitive to one part in one million. Quantitative determination of 5-hydroxymethylfurfural: gravimetric, colorimetric, titrimetric (*Troje*, Z.Ver. deut.Zucker-Ind. **1925**, 635). Because of its relation to the hexoses it is used in certain tests in food chemistry: the Selivanov reaction for the detection of hexoses, the Fiehe reaction for the differentiation of artificial and natural honey (*Troje*, Z.Ver.deut.Zucker-Ind. **1925**, 635), the Baudouin reaction for the differentiation of butter and margerine (*van Ekenstein, Blanksma*, Ber. **43**, 2355).

The corresponding halogen derivatives, **5-chloromethylfurfural** and **5-bromomethylfurfural**, $(C_4H_2O)(CH_2Br)CHO$, m.p. 60°, are prepared by the action of HCl and HBr on ketoses or cellulose (*Fenton*, Ber. **43**, 2795).

Ketones

2-Acetylfuran, *2-furyl methyl ketone*, m.p. 33°, b.p. 67° (10 mm.), occurs in wood tar and is synthesized from ethyl furoylacetate, $C_4H_3O(COCH_2CO_2C_2H_5)$, b.p. 143° (10 mm.), which is the condensation product of pyromucic acid ester and acetic ester (*Torrey, Zanetti*, Am.Chem.J. **44**, 391; *Zanetti, Beckmann*, Am. **50**, 1438). **2-Furylacetone**, $(C_4H_3O)CH_2COCH_3$, b.p. 180° (*Darzens*, C.r. **142**, 214). **2-Benzoylfuran**, $C_4H_3O(COC_6H_5)$, b.p. 164° (19 mm.), is prepared from pyromucic acid chloride, benzene, and aluminum chloride (*Marquis*, Bull. [III] **23**, 32). **2,5-Dibenzoylfuran**, $C_4H_2O(COC_6H_5)_2$, m.p. 107°, from dehydromucic acid chloride (see below), benzene and aluminum chloride. **2-Phenyl-5-methyl-3-acetylfuran**, m.p. 57°, from phenacyldiacetylmethane (*March*, C.r. **134**, 843).

Carboxylic Acids

A general synthesis for furancarboxylic acids, adapted from pyrrole chemistry, consists in the action of *as*-dichloro ethers on β-ketonic acid esters (*Fujita*, J.Pharm.Soc.Japan **1925**, #519, 4).

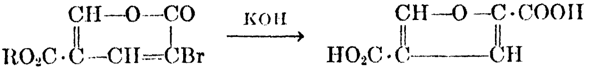
2-**FUROIC ACID, pyromucic acid,** m.p. 134° with sublimation, is prepared by the oxidation of furfural and by the distillation of mucic acid or isosaccharic acid.

History.—*Scheele*, in 1780, observed pyromucic acid as a product of the distillation of mucic acid. *Pelouze*, in 1834, determined its composition, and in 1877 *v. Baeyer* established its constitutional formula.

Ethyl ester, m.p. 34°, b.p. 210°. **Chloride,** b.p. 170° (*Baum*, Ber. **37**, 2951). **Amide,** m.p. 142°, is converted by PCl_3 to **furonitrile,** which is also produced from furaldoxime by loss of water [*Yamaguchi*, Bull.Chem.Soc.Japan **1** (1926), 35]. **Anhydride,** m.p. 73° (*Baum*, Ber. **34**, 2505). **Hydrazide,** m.p. 80°. **Azide,** m.p. 62° (*Leimbach*, J.pr. **65**, 20).

Bromine vapor converts 2-furoic acid to a tetrabromide, $C_4H_3Br_4O \cdot COOH$, which is oxidized by chromic acid to dibromosuccinic acid. Evaporation of 2-furoic acid with bromine water yields fumaric acid; if an excess of bromine or chlorine water is present, mucobromic or mucochloric acid (Vol. I, p. 457) is formed. Heating the tetrabromide or brominating 2-furoic acid in glacial acetic acid results in the formation of **5-bromo-2-furoic acid,** $C_4H_2BrO \cdot COOH$, m.p. 184° (*Hill, Sanger*, Ann. **232**, 42). 3-**Bromo-2-furoic acid,** m.p. 129°, is obtained from two dibromo-2-furoic acids (*Hill, Sanger*, Ber. **17**, 1759) by treatment with zinc. 2-Furoic acid is eliminated from the human body as *pyromucuric acid*, N-2-furoylglycine, $C_4H_3O \cdot CO \cdot NH \cdot CH_2COOH$, m.p. 165° (*Schlempp*, Z.physiol. Chem. **117**, 368).

2,5-Furandicarboxylic acid, dehydromucic acid, $C_4H_2O \cdot (CO_2H)_2$, is prepared by heating mucic acid or saccharic acid with hydrochloric acid, concentrated hydrobromic acid, or concentrated sulfuric acid. It is sparingly soluble in water. It decomposes on heating into carbon dioxide and 2-furoic acid. The esters are all solid, and show interesting melting point regularities. **Dimethyl ester,** m.p. 112°, b.p. 155° (15 mm.). **Diethyl ester,** m.p. 47°, b.p. 168° (15 mm.). **Chloride,** m.p. 80°. Unlike 2-furoic acid, 2,5-furandicarboxylic acid is readily reduced by sodium amalgam to a dihydro acid [*Hill*, Am.Chem.J. **25** 439; *Yoder, Tollens*, Ber. **34**, 3446]. **2,4-Furandicarboxylic acid,** m.p. 266°, is produced by the action of potassium hydroxide on the esters of 3-bromocoumalic acid (*Feist*, Ber. **34**, 1992):



Dimethyl ester, m.p. 110°.

Homologous furancarboxylic acids are synthesized from γ-dioxocarboxylic acids by loss of water. **5-Methyl-2-furoic acid,** m.p. 109°, is prepared by oxidation of methylfuraldehyde; its chloride, m.p. 28°, b.p. 202°, is brominated in the side-chain, and yields a dibromo product which can be hydrolyzed to **5-formyl-2-furoic acid,** $C_4H_2O(COOH)(CHO) + H_2O$, m.p. 202°. On oxidation the latter is converted to 2,5-furandicarboxylic acid (*Hill, Sawyer*, Am.Chem.J. **20**, 169). Bromine water attacks the ring of methylfuroic acid, producing acetylacrylic acid, $CH_3COCH{:}CH \cdot COOH$ (*Hill, Hendrixson*, Ber. **23**, 452).

2,5-DIMETHYL-3-FUROIC ACID, pyrotritaric acid, uvinic acid, m.p. 135°, is prepared (*1*) from the ester of acetonylacetoacetic acid (Vol. I, p. 603), (*2*) from 2,5-dimethylfuran-3,4-dicarboxylic acid and 2-methyl-5-carboxymethyl-3-furoic acid (see below) by decarboxylation, (*3*) from tartaric acid by dry distillation, and (*4*) from pyruvic acid by boiling with aqueous barium hydroxide or sodium acetate for a long time (besides uvitinic acid). Heating in water at 150–160° decomposes it to carbon dioxide and acetonylacetone; rapid heating by itself converts it to dimethylfuran (p. 16).

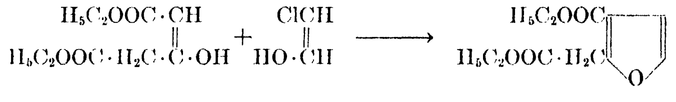
2,4-Dimethyl-3-furoic acid, m.p. 122°, is prepared (*1*) from bromodimethylcoumalic acid, instead of the expected 2,4-dimethylfuran-3,5-dicarboxylic acid, (*2*) from acetoacetic ester by condensation with chloroacetone, and (*3*) from the condensation product of β-oxoglutaric acid and chloroacetone, **2-carboxymethyl-4-methyl-3-furoic acid**, $C_4HO(CH_3)(CH_2 \cdot CO_2H)(CO_2H)$, m.p. 196°, by decarboxylation (*Feist*, Ber. **35**, 1545). The latter acid is isomeric with methronic acid (see below).

2-Methyl-5-phenyl-3-furoic acid, m.p. 181°, from acetophenoneacetoacetic ester, $C_6H_5 \cdot CO \cdot CH_2 \cdot CH(CO_2R)CO \cdot CH_3$, (*Paal*, Ber. **17**, 2764), decomposes on heating into carbon dioxide and methylphenylfuran.

2,5-Dimethylfuran-3 4-dicarboxylic acid, carbopyrotritaric acid, m.p. 261°, is obtained from diacetylsuccinic acid ester by boiling with dilute sulfuric acid (*Knorr*, Ber. **17**, 2864; **22**, 146). At elevated temperatures it decomposes into carbon dioxide and 2,5-dimethyl-3-furoic acid.

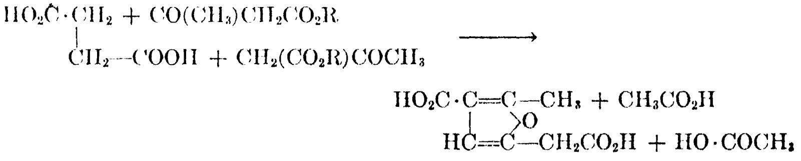
2-Furylacetic acid, m.p. 67° (*Runde, Scott, Johnson*, Am. **52**, 1287).

The **diethylester** of **2-carboxymethyl-3-furoic acid** (free acid, m.p. 217–218°) is formed by the reaction of the diethyl ester of β-oxoglutaric acid and α,β-dichloroethyl ethyl ether, which enters the reaction as chloroacetaldehyde (*Reichstein, Zschokke*, Helv.Chim.Acta **15**, 268)



2-Phenyl-3-furoic acid, m.p. 163°, is prepared from the ester of benzoylacetic acid by a similar reaction.

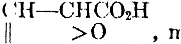
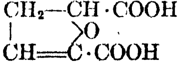
5-Carboxymethyl-2-methyl-3-furoic acid, *methronic acid*, m.p. 204°, is isomeric with carbopyrotritaric acid, and, like the latter, yields 2,5-dimethyl-3-furoic acid on decarboxylation. It is prepared: (*1*) From acetoacetic ester and sodium succinate in the presence of acetic anhydride (*Fittig*, Ber. **18**, 3410). The reaction can be formulated in this way (*Schroeter*, Ber. **39**, 2129):



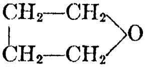
For another possible course of this synthesis, see *Trefiljev*, J.chim.Ukraine **1** (1925), 121.

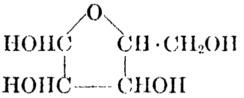
By a similar reaction acetoacetic ester and pyrotartaric acid form methylmethronic acid.

(*2*) 5-Carboxymethyl-2-methyl-3-furoic acid is also formed in the condensation of acetoacetic ester with glyoxal, together with 2-methylfurylacetic acid (*Polonowsky*, Ann. **246**, 1; *Knorr*, Ber. **22**, 152; *Fittig*, Ann. **250**, 166).

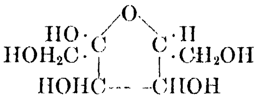
HYDROFURANS. Only a few hydrofuran derivatives have been obtained by reduction of furans, for example, **tetrahydro-2-methyl-5-phenylfuran**, b.p. 230°, from methylphenylfuran (p. 16), and **tetrahydrodiphenylfuran** (*Perkin, Schlösser*, J. **57**, 944). α- or *cis*-**Dihydrofuran-2,5-dicarboxylic acid**,  $\begin{matrix} CH-CHCO_2H \\ \| \quad >O \\ CH-CHCO_2H \end{matrix}$, m.p. 150, is formed by the reduction of 2,5-furandicarboxylic acid (p. 20) with sodium amalgam in carbon dioxide at 0°; in alkaline solution it rearranges to the β- or *trans*-acid, m.p. 179°. The latter can be resolved by cinchonine into its optically active components, m.p. 144°. With bromine, both acids give dibromides, which are converted to 2-furoic acid by barium hydroxide solution. Long boiling with alkali rearranges both the α- and the β-acid to γ- or **2,3-dihydrofurandicarboxylic acid**,  $\begin{matrix} CH_2-CH \cdot COOH \\ | \quad >O \\ CH=C \cdot COOH \end{matrix}$; unlike the α- and β-acids, this acid is further reduced by sodium amalgam to **tetrahydrofuran-2,5-dicarboxylic acid,** α-form, m.p. 95°, β-form, m.p. 124° (*Hill,* Am.Chem.J. **25,** 439; *Hill, Russe, ibid.* **33,** 372).

Dihydrofuran, b.p. 67°, is synthesized by the reduction of erythritol; it is converted to furan by PCl_5 (*Henninger,* Bull. [II] **35,** 418). **2-Methyldihydrofuran** is prepared from acetylpropyl alcohol (Vol. I, p. 395; *Lipp,* Ber. **22,** 1196). **2,5-Diphenyldihydrofuran,** m.p. 89°, is obtained from α-phenylcinnamenylacrylic acid dibromide (2,5-diphenyl-2,5-dibromo-3-pentenoic acid) with alkali (*Thiele, Rössner,* Ann. **306,** 210). Other **dihydrofuran** derivatives have been synthesized from α-chlorocrotonic acid ester and chlorofumaric acid ester by condensation with the sodium derivatives of acetoacetic ester and of benzoylacetic ester (*Ruhemann, Wolf,* J. **69,** 1383).

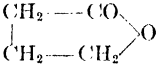
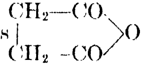
Tetramethylene oxide, *tetrahydrofuran,*  and its derivatives are obtained from 1,4-glycols or the corresponding unsaturated compounds, by catalytic hydrogenation (*Fittig,* Ann. **303,** 168; *Kariyone,* J.Pharm.Soc.Japan **1925,** No. 515, 1; C. **1925,** I, 2376). The 1,4-oxide forms of the pentoses and hexoses, such as fructofuranose and glucofuranose, are derivatives of this tetrahydrofuran (Vol. I, p. 693; *Goodyear, Haworth,* J. **1927,** 3136):

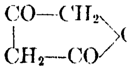
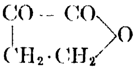
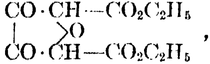


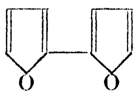
1,4-Pentose



2,5-Hexose

γ-Lactones, such as butyrolactone,  and the anhydrides of the succinic acid series, such as  are *oxo-* and *dioxotetrahydrofurans.*

Tetronic acid,  (Vol. I, p. 599), and its derivatives, and α-oxolactones of the formula  which result from the condensation of α-oxo acids with aldehydes, are also dioxotetrahydrofurans (*Erlenmeyer, Lux,* Ber. **31,** 2218). The **diethyl ester of 3,4-dioxotetrahydrofuran-2,5-dicarboxylic acid,**  , m.p. 189°, is formed by the condensation of oxalic ester and diglycolic acid diethyl ester by means of sodium ethylate (*Johnson, Johns,* Am.Chem.J. **36,** 290).

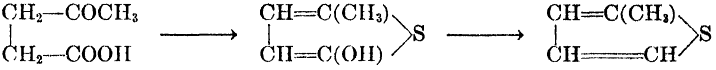
2,2′-Difuryl,  , b.p. 65° (7 mm.), has been obtained by condensation of 2-furoylacetic ester and chloroacetaldehyde and decarboxylation of the acid formed (*Kondo, Suzuki,* J.Pharm.Soc.Japan **1927,** No. 544, 70; C. **1927,** II, 1027).

2. THIOPHENES

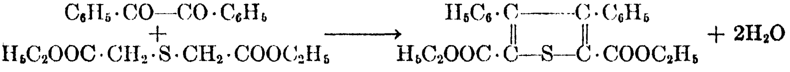
Thiophene, C_4H_4S, the sulfur analogue of furan, is very similar to benzene in its behavior (see p. 15). Its ring can be regarded as a benzene ring in which one of the three vinylene groups has been replaced by sulfur. It was named "thiophene" because of its similarity to benzene, thio indicating the presence of sulfur, and phene, the relationship with phenyl compounds. A structural formula analogous to the *Thiele* formula for benzene has been postulated for thiophene (see p. 15). Spectroscopic data for thiophene and its derivatives support this hypothesis of a ring with complete inner saturation (*v. Auwers, Kohlhaas,* J.pr. **108,** 321). Thiophene and its alkyl derivatives not substituted in the 2-position give a dark blue color reaction with isatin and concentrated sulfuric acid, which is known as the *indophenine reaction* (*Meyer,* Ber. **16, 1473**; for details, see p. 25).

History.—Thiophene and methylated thiophenes are invariably present in the benzene hydrocarbons obtained commercially from coal tar. Because of this, before the discovery of thiophene, the indophenine reaction was considered to be characteristic of benzene hydrocarbons. In 1883 *Victor Meyer* observed that this reaction was not given by benzene prepared from benzoic acid, and was caused by an impurity containing sulfur in the commercial benzene. In this way thiophene was discovered, and subsequent investigations by *Meyer* disclosed its constitution and its kinship with furan and pyrrole. Thionessal, a derivative of thiophene, had been known earlier (*Laurent,* 1841), but its identity with tetraphenylthiophene was not uncovered until 1891 (*Baumann, Fromm*).

The synthesis of thiophene derivatives from γ-dicarbonyl compounds has already been discussed on p. 15. The conversion of γ-oxo acids to hydroxythiophenes with P_2S_5 takes place very readily; the hydroxythiophenes are reduced by P_2S_3 to thiophenes (*Paal,* Ber. **19,** 551; *Paal, Hoffmann,* Ber. **23,** 1495):

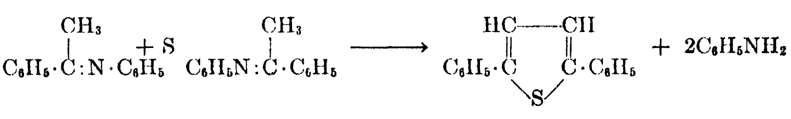

Levulinic acid
2-Hydroxy-5-methylthiophene
2-Methylthiophene

A new synthesis of thiophene derivatives consists in the ring closure of a 1,2-dicarbonyl compound, such as benzil, and a thiodiacetic acid ester under the influence of sodium ethylate (*Hinsberg,* Ber. **43,** 901; **45,** 2413):



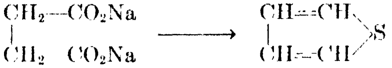
For the preparation of hydroxythiophenes from α-chloroacetyl-β-aminocrotonic acid ester and pure potassium hydrosulfide, see *Benary, Silberström,* Ber. **52,** 1605.

Thiophene and its derivatives are produced in several pyrogenous reactions. 2,5-Diarylthiophenes are formed when anils of aromatic-aliphatic ketones (such as the anil of acetophenone) are heated with sulfur at 220° (*Bogert, Herrera,* Am. **45,** 238).



Alkenylbenzenes on heating with sulfur yield phenylthiophenes. Styrene gives diphenylthiophene, stilbene gives tetraphenylthiophene, and acetylenedicarboxylic acid gives thiophenetetracarboxylic acid (*Michael,* Ber. **28,** 1635; *Baumann, Fromm,* Ber. **30,** 110).

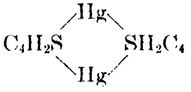
THIOPHENE, C_4H_4S, m.p. —29.8°, b.p. 84°, d^{23} 1.062, occurs in coal tar, together with methylthiophenes; thiophene and its homologues are present in the corresponding technical benzene hydrocarbons (about 0.6%), since thiophene and benzene have approximately the same boiling points, as do also methylthiophene and toluene, and so forth. Thiophene is formed in good yield from sodium succinate on heating with P_2S_3 (*Volhard, Erdmann*, Ber. **18**, 454):



Other compounds, such as crotonic acid, butyric acid, and paraldehyde, also give thiophene when heated with P_2S_3. It is obtained by passing ethyl sulfide, or acetylene and H_2S, through a glowing tube (*Meyer, Wesche*, Ber. **50**, 422; *Tomkinson*, J. **125**, 2264), illuminating gas over pyrite (FeS_2) at 280 to 310° (*Steinkopf, Kirchhoff*, Ann. **403**, 1; *Steinkopf*, Ann. **430**, 78), or acetylene or ethylene over boiling sulfur.

Thiophene is removed from technical benzene by shaking with a little concentrated sulfuric acid (4–10%) (*Weitz*, Ber. **17**, 792), or by precipitating as thiophenemercury hydroxyacetate, $C_4H_2S(HgOCOCH_3)\cdot HgOH$, by boiling with mercuric acetate. The mercury compound is split into thiophene and mercuric chloride by boiling hydrochloric acid (*Dimroth*, Ber. **32**, 758; *Schwalbe*, Ber. **38**, 2208). Thiophene is determined quantitatively as methyl thienyl ketone (*Stadnikow, Goldfarb*, Ber. **61**, 2341).

Thiophene is a colorless liquid with an odor similar to benzene. It crystallizes in a bath of solid carbon dioxide and ether. It is not attacked by sodium even when boiled with it. It forms characteristic, crystalline salts with mercuric chloride, which are useful in the identification of thiophene, and also of its homologues: C_4H_3SHgCl, $C_4H_2S(HgCl)_2$ (*Steinkopf, Bauermeister*, Ann. **403**, 50; *Steinkopf*, Ann. **413**, 310; **428**, 23). The compound containing two mercury atoms is transformed in dilute pyridine solution in the presence of sodium iodide to a derivative with mercury in the ring (*Steinkopf, Bielenberg, Augestad-Jensen*, Ann. **430**, 63):



2-Thienylmagnesium iodide reacts with $SnCl_4$ to form *tetra-2-thienyltin*, $[C_4H_3S]_4Sn$, m.p. 153°, and with $PbCl_2$ to form *tetra-2-thienyllead*, m.p. 152° (*Krause, Renwanz*, Ber. **60**, 1582).

According to its formula thiophene is a cyclic diolefin sulfide, but it exhibits none of the ease of addition of alkyl sulfides for methyl iodide, oxygen, etc. It is readily attacked by permanganate. Concentrated nitric acid converts it in a vigorous reaction to dinitrothiophene.

Diazoacetic ester reacts with thiophene just as it does with benzene (*Steinkopf, Augestad-Jensen*, Ann. 428, 154).

Benzene series	B.p.	Thiophene series	B.p.
Benzene	80.5°	Thiophene	84°
Toluene	110.3°	2-Methylthiophene	113°
p-Xylene	138°	2,5-Dimethylthiophene	135°
Isopropylbenzene	153°	2-Isopropylthiophene	154°
Diphenyl	254°	Dithienyl	266°
Diphenylmethane	261°	Dithienylmethane	267°
Chlorobenzene	132°	2-Chlorothiophene	130°
p-Dichlorobenzene	172°	2,5-Dichlorothiophene	170°
Bromobenzene	155°	2-Bromothiophene	150°
Tetrabromobenzene	329°	Tetrabromothiophene	326°
p-Dinitrobenzene	299°	Dinitrothiophene	290°
Benzoic acid	250°	2-Thiophenecarboxylic acid	260°
Benzonitrile	191°	Cyanothiophene	190°
Acetophenone	202°	Methyl thienyl ketone	213°
Benzophenone	307°	Dithienyl ketone	326°
Cinnamic acid	m.p. 133°	Thienylacrylic acid	m.p. 138°

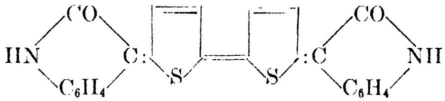
The striking similarity in physical properties between members of the thiophene series and those of the benzene series is illustrated in the table of boiling points and melting points on page 24.

The analogy in chemical behavior between these two series of compounds will be made apparent in the following discussions of thiophene derivatives. The analogy extends to physiological activity; the benzene ring in compounds such as cocaine, atropine, and eucaine can be replaced by a thiophene ring with little effect on their action (*Steinkopf, Ohse*, Ann. **437**, 14; *Steinkopf, Wolfram, ibid.* **437**, 22; *Steinkopf, Ohse*, Ann. **448**, 205). Thiophene-2-carboxylic acid is eliminated by the human body as *thiophenuric acid*, which corresponds to hippuric acid of the benzene series (*Schempp*, Z.physiol.Chem. **117**, 41).

Indophenine Reaction

This color reaction, mentioned on p. 23, is best carried out in this way (*Schlenk, Blum*, Ann. **433**, 98): A drop of thiophene, or a corresponding amount of the solution to be tested for thiophene, is added to a bright yellow chloroform solution of isatin. This solution is ice-cooled, and pure, ice-cold, concentrated sulfuric acid is added. A blue-green coloration results in the presence of even the smallest trace of thiophene.

The color is due to an indigo dye formed from two molecules of thiophene and two molecules of isatin [*Schlenk, Blum*, Ann. **433**, 95; *Heller*, Z.angew.Chem. **37** (1924), 1017]:



In agreement with this structure 2-alkyl- and 2,5-dialkylthiophene do not give the indophenine reaction.

The color reaction produced with thiophene is not restricted to isatin, but takes place under similar conditions with other compounds containing the grouping ·CO·CO·, such as benzil and phenanthraquinone (*Laubenheimer* reaction, *Oster*, Ber. **37**, 3348). Mesoxalic acid ester reacts in the same way with thiophene (*Schlenk, Blum*, Ann. **433**, 95).

1. **HOMOLOGUES OF THIOPHENE.** (The numbering of the thiophene ring is analogous to that of the furan ring, see p. 15.) Homologues of thiophene, in addition to their synthesis from 1,4-dicarbonyl compounds, are obtained from thiophene by methods similar to those used in the preparation of benzene homologues from benzene, such as treatment of iodothiophene with alkyl iodides and sodium, or of thiophene with alkyl bromides and $AlCl_3$. A number of thiophene homologues have been found in shale tar oil [*Scheibler*, Z.angew.Chem. **39** (1926), 1397]. Alkylthiophenes, like their benzene analogues, yield carboxylic acids on oxidation.

2-Methylthiophene, α-thiotolene, b.p. 113°, prepared from iodothiophene and methyl iodide with sodium or synthetically from levulinic acid [see p. **23**; *Chrzaszczlzewska*, Roczniki Chem. **5** (1926), 33], gives thiophene-2-carboxylic acid on oxidation. **3-Methylthiophene, β-thiotolene,** b.p. 114°, from sodium pyrotartrate and P_2S_3. Both methylthiophenes are present in coal tar toluene. **Dimethylthiophenes** or **thioxenes** are found in crude xylene (*Keiser*, Ber. **29**, 2560). **2,3-Dimethylthiophene,** b.p. 136°. **2,4-Dimethylthiophene,** b.p. 138°. **2,5-Dimethylthiophene,** b.p. 135°. **3,4-Dimethylthiophene,** b.p. 145°. **2-Isopropylthiophene,** b.p. 154°, is obtained from thiophene and isopropyl bromide with aluminum chloride.

2-Phenylthiophene, m.p. 41°, from β-benzoylpropionic acid (*Kues, Paal*, Ber. **19**, 3141). **2,5-Diphenylthiophene,** m.p. 153°, is prepared from diphenacyl with P_2S_5, from styrene or cinnamic acid with sulfur (*Baumann, Fromm*, Ber. **28**, 890), or from the anil of acetophenone with sulfur (*Bogert, Herrera*, Am. **45**, 238). **3,4-Diphenylthiophene,** m.p. 114°. **2,4-Diphenylthiophene,** m.p. 119°, is formed with the **2,5**-diphenyl derivative when cinnamic acid is heated with sulfur (*Fromm,* *Fantl, Leibsohn*, Ann. **457**, 267). **Tetraphenylthiophene, thionessal,** m.p. 184°, is obtained by heating thiobenzaldehyde or sodium thiobenzoate, and from stilbene and sulfur, as thiophene is prepared from ethylene and sulfur (*Laurent*, Ann. **38**, 320; *Baumann, Klett*, Ber. **24**, 3310; *Fromm, Achert*, Ber. **36**, 534).

2,2′-**Dithienyl**, m.p. 33°, is formed from thiophene by the action of H_2SO_4 and from 2-iodothiophene with silver (*Eberhard*, Ber. **28**, 2385). 3,3′-**Dithienyl**, m.p. 132°, from butane-$\alpha,\beta,\gamma,\delta$-tetracarboxylic acid with P_2S_3. A mixture of the two dithienyls results when thiophene vapor is passed through an incandescent tube. **Dithienylmethane**, $(C_4H_3S)_2CH_2$, m.p. 43°, b.p. 267°, from thiophene and methylal. **Thienyldiphenylmethane**, $(C_4H_3S)\cdot CH(C_6H_5)_2$, m.p. 63°, b.p. 335°, from thiophene and benzohydrol. **Thienyltriphenylmethane**, $(C_6H_5)_3C(C_4H_3S)$, m.p. 237°, is obtained from triphenylmethanol and thiophene with P_2O_5; the homologues of thiophene also condense with triphenylmethanol under the same conditions (*Weisse*, Ber. **29**, 1402). **Dithienylphenylmethane**, $C_6H_5CH(C_4H_3S)_2$, m.p. 75°, is formed by the condensation of benzaldehyde and thiophene (*Töhl, Nahke*, Ber. **29**, 2205). *as*-**Dithienylethane**, $CH_3CH(C_4H_3S)_2$, b.p. 270–280°, *s*-**dithienylethylene**, $(C_4H_3S)CH:CH(C_4H_3S)$, m.p. 125° (*Nahke*, Ber. **30**, 2041).

2. HALOGEN DERIVATIVES. Thiophene is attacked by chlorine and bromine in the cold, even more energetically than benzene is. Iodine also reacts with thiophene at room temperature if HgO is present. All three halogens first enter the 2-position. For the preparation of pure monobromothiophene, N-bromoacetamide or cyanogen bromide is used (*Steinkopf*, Ann. **430**, 78). Oxidation of brominated thiophene with very cold concentrated nitric acid ruptures the ring, yielding products such as dibromomaleic acid, bromocitraconic acid, and dibromoacetoacrylic acid (*Angeli, Ciamician*, Ber. **24**, 74, 1347).

2-Alkylthiophenes are chlorinated and brominated almost exclusively in the nucleus, even in the sunlight and at the boiling point. 3-Methylthiophene, on the contrary, is halogenated mostly in the side-chain, especially when the reaction mixture is heated.

2-**Chlorothiophene**, b.p. 130° (*Steinkopf, Otto*, Ann. **424**, 61). 2,5-**Dichlorothiophene**, b.p. 170°. **Tetrachlorothiophene**, C_4Cl_4S, m.p. 36°, b.p. 220–240°. 2-**Bromothiophene**, b.p. 150°. 2,5-**Dibromothiophene**, b.p. 211° (*Steinkopf, Otto*, Ann. **424**, 61); the formation of this compound can serve for the separation by means of bromine of all the thiophene present in a crude benzene (*Stadler*, Ber. **18**, 1490). **Tribromothiophene**, m.p. 29°, b.p. 260°. **Tetrabromothiophene**, m.p. 112°, b.p. 326°, is also produced in the energetic bromination of substituted thiophenes when the substituents are displaced (*Marcusson*, Ber. **26**, 2457). 2-**Iodothiophene**, b.p. 182° (*Thyssen*, J.pr. **65**, 5).

3. NITROTHIOPHENES. Nitric acid attacks thiophene very energetically. To moderate the reaction a mixture of thiophene vapor and air is passed into fuming nitric acid; the products are mono- and dinitrothiophene (*Meyer, Stadler*, Ber. **17**, 2648). Nitration with benzoyl nitrate (Vol. III, p. 298) in carbon tetrachloride (*Francis*, Ber. **39**, 3801) or with glacial acetic acid-acetic anhydride as the diluent (*Babasinian*, Am. **50**, 2748) runs smoothly.

2-**Nitrothiophene**, m.p. 44°, b.p. 225°. **Dinitrothiophene**, m.p. 52°, b.p. 290°; its alcoholic solution turns dark red when alkali is added. This color reaction can be used to test technical dinitrobenzene for the presence of dinitrothiophene (*Meyer, Stadler*, Ber. **17**, 2778).

4. AMINOTHIOPHENES. Nitrothiophenes are reduced much less readily than the nitrobenzenes. 2-Nitrothiophene in dilute alcoholic solution is reduced by zinc and hydrochloric acid to 2-thiophenine (*Stadler*, Ber. **18**, 1490).

2-**Thiophenine, 2-aminothiophene,** b.p. 79° (11 mm.), is a bright yellow oil which resinifies on exposure to air. Its hydrochloride forms deliquescent needles. It can be diazotized in the form of its tin double salt (*Steinkopf, Müller*, Ann. **448**, 210). Thiophenine couples with salts of diazobenzene to form azo dyes such as, $C_6H_5N:N\cdot C_4H_2S\cdot NH_2$ (*Stadler*, Ber. **18**, 2316). 2-Acetamidothiophene, $(C_4H_3S)NHCOCH_3$, is also obtained from the oxime of methyl thienyl ketone, $(C_4H_3S)\cdot C(NOH)CH_3$ (p. 27), by the Beckmann rearrangement [*Rimini*, Chem.Z. **23** (1899), 266]. 2-Thienylurethan, $(C_4H_3S)NHCO_2C_2H_5$, m.p. 48°, prepared from the azide of thiophene-2-carboxylic acid, decomposes on saponification (*Thyssen*, J.pr. **65**, 1).

5. SULFONIC ACIDS. Like the benzenesulfonic acids, thiophenesulfonic acids are produced by treatment of thiophene with sulfuric acid, but the reaction must be moderated by dilution of the thiophene with petroleum ether, benzene or the like. They are also obtained from thienyl ketones by displacement of the ketone group by the sulfonic acid group (*Krekeler*, Ber. **19**, 674; *Muhlert*, Ber. **19**, 1620; *Keiser*, Ber. **29**, 2562).

6. HYDROXYTHIOPHENES. Hydroxythiophene is not known. **2-Hydroxy-5-methylthiophene, hydroxythiotolene,** $C_4H_2(CH_3)(OH)S$, is synthesized from levulinic acid (p. 23). **2-Thiophenethiol,** $(C_4H_3S)SH$, b.p. 166°, is prepared by reduction of 2-thienylsulfonyl chloride, $(C_4H_3S)SO_2Cl$; it is present in the crude thiophene obtained by distilling succinic acid with P_2S_5.

7. ALCOHOLS. 2-Thienylmethanol, b.p. 207°; for its preparation, see below. Tertiary 2-thienylmethanols, $(C_4H_3S)C(OH)R_2$, such as **dimethyl-, methylphenyl-,** and **diphenyl-2-thienylmethanol,** m.p. 33°, 50°, and 125°, are produced by the reaction of 2-thienylmagnesium iodide, $(C_4H_3S){\cdot}MgI$, with ketones (*Thomas*, C.r. **146**, 642).

8. ALDEHYDES AND KETONES. 2-Thiophenecarboxaldehyde, b.p. 198°, is prepared by the reaction of 2-thienylmagnesium iodide with orthoformic acid ester [*Grischkewitsch-Trochimovski*, J.Russ.Phys.-Chem.Soc. **43** (1911), 204]. It is obtained in smaller yield by the catalytic reduction of thiophene-2-carboxylic acid chloride [Vol. I, p. 226; *Rojahn, Schultin*, Arch.Pharm. **264**, (1926), 348], by heating thienylglyoxylic acid (see below) and by the reaction of α-chloroglutaconaldehyde, $CHO{\cdot}CCl{:}CH{\cdot}CH_2CHO$, with hydrogen sulfide (*Dieckmann*, Ber. **38**, 1651). The aldehyde is oxidized to thiophene-2-carboxylic acid by the oxygen of the air. With aqueous potassium hydroxide it forms, like benzaldehyde and furfuraldehyde, the corresponding carboxylic acid and alcohol:

$$2C_4H_3S{\cdot}CHO + KOH = C_4H_3S{\cdot}CO_2K + C_4H_3S{\cdot}CH_2(OH)$$

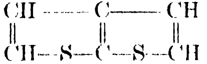
With sodium acetate and acetic anhydride it condenses to thienylacrylic acid, $C_4H_3S{\cdot}CH{:}CH{\cdot}CO_2H$, m.p. 138°, which is analogous to cinnamic acid. With ammonia it gives a hydramide, $(C_5H_4S)_3N_2$, m.p. 111°, corresponding to hydrobenzamide (Vol. III, p. 272). A *thiophene green* is formed by a process similar to that which converts benzaldehyde to malachite green.

The ketone derivatives of thiophene are readily obtained from acid chlorides and thiophene in the presence of aluminum chloride, phosphorus pentoxide (*Steinkopf, Schubart*, Ann. **424**, 1), or tin tetrachloride (*Stadnikoff, Rakowsky*, Ber. **61**, 268). **2-Thienyl methyl ketone,** *acetothienone*, $C_4H_3S{\cdot}COCH_3$, b.p. 213°, is oxidized by permanganate first to **thienylglyoxylic acid,** $C_4H_3S{\cdot}CO{\cdot}CO_2H$, m.p. 91°, then to thiophene-2-carboxylic acid. **2-Thienyl ethyl ketone,** b.p. 100° (11 mm.); **2-thienyl propyl ketone,** b.p. 120° (16 mm.); **2,5-dimethyl-3-thienyl methyl ketone,** b.p. 126° (18 mm.) (*Steinkopf, Schubart*, Ann. **424**, 18). **Dithienyl ketone, thienone,** $CO(C_4H_3S)_2$, m.p. 88°, b.p. 326°, is prepared from thiophene and $COCl_2$. **2-Thienyl phenyl ketone,** m.p. 55°, b.p. 360°, from thiophene, benzoyl chloride, and aluminum chloride.

9. THIOPHENE CARBOXYLIC ACIDS. The carboxylic acids of thiophene are formed by the methods used in the preparation of aromatic carboxylic acids: (*1*) By oxidation of alkylthiophenes with alkaline permanganate (2-ethylthiophene first forms thienylglyoxylic acid, then thiophene carboxylic acid). (*2*) From iodo- or bromothiophene with chloroformic acid ester and sodium, or from thiophene with chloroformic acid ester or urea chloride and aluminum chloride.

Thiophene-2-carboxylic acid, m.p. 126°, b.p. 260°, K (dissociation constant) = 0.0302, is obtained from 2-iodothiophene and chloroformic acid ester with Na amalgam, from thienyl methyl or ethyl ketone, $(C_4H_3S)COC_2H_5$, by oxidation with permanganate (*Thyssen*, J.pr. **65**, 6) and from mucic acid by heating with barium sulfide (p. 15). Its nitrile, $C_4H_3S{\cdot}CN$, is formed by distillation of 2-thiophenesulfonic acid with KCN or by removal of water from thiophene aldoxime (*Douglas*, Ber. **25**, 1311). *Ethyl ester*, b.p. 115° (25 mm.); *chloride*, b.p. 203°; *hydrazide*, m.p. 136°; *azide*, m.p. 37° (*Thyssen*, J.pr. **65**, 1). For the substitution of thiophene-2-carboxylic acid for benzoic acid in pharmacologically active compounds, see *Steinkopf, Ohse*, Ann. **437**, 14, and *Steinkopf, Wolfram*, Ann. **437**, 22. **Thiophene-3-carboxylic acid,** m.p. 138°, from 3-methylthiophene. **Thiophene-2,3-dicarboxylic acid,** m.p. 260° (dec.), condenses with resorcinol, as phthalic acid does, to form a fluorescein. 2,4-Acid, m.p. 118°; the 2,5-acid sublimes at 300° and is reduced by Na amalgam to **tetrahydrothiophene-**

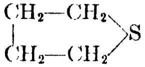
2,5-dicarboxylic acid, m.p. 162°, which reduces warm ammoniacal silver solution and in general behaves like hydrophthalic acid (*Ernst*, Ber. **19**, 3274). **Thiophenetetracarboxylic acid methyl ester,** m.p. 127°, is prepared by heating the methyl ester of acetylenedicarboxylic acid with sulfur in a tube at 150–155° (*Michael*, Ber. **28**, 1635).

Thiophthene, 

$$\begin{array}{ccccc} CH & — & C & — & CH \\ \| & & \| & & \| \\ CH—S— & & C & & —S—CH \end{array}$$

, b.p. 225°, is formed by heating citric acid with P_2S_3, by the pyrogenic reaction of sulfur and acetylene (*Biedermann, Jacobson*, Ber. **19**, 2444) and, to some extent, by heating thiophene at 650° (*Meyer, Wesche*, Ber. **50**, 423; *Peel, Robinson*, J. **1928**, 2068).

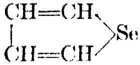
TETRAHYDROTHIOPHENE, TETRAMETHYLENE SULFIDE,



and its homologues are prepared from 1,4-dihalogen paraffins by treatment with K_2S (*v. Braun, Trümpler*, Ber. **43**, 545; *v. Braun*, Ber. **43**, 3220).

3. SELENOPHENES

The selenophenes have a structure similar to that of the thiophenes, but with a selenium atom in place of the sulfur atom.

SELENOPHENE,  yellowish liquid, b.p. 148° (250 mm.), is prepared by heating sodium succinate with phosphorus triselenide (*Foa*, Gazz. **39** II, 527) and also by passing ethyl selenide through an incandescent tube (*Meyer* Ber. **18**, 1772). **2,5-Dimethylselenophene, selenoxene,** b.p. 153°, is formed from acetonylacetone with phosphorus selenide (*Paal*, Ber. **18**, 2255). For the preparation of 2,4-diarylselenophenes, see *Bogert, Herrera*, Am. **45**, 238. **2,4-Diphenylselenophene,** m.p. 112°. With isatin and sulfuric acid selenophenes turn carmine-red; they also give the *Laubenheimer* reaction (p. 25). **Tetrahydroselenophene**: *Morgan, Burstall*, J. **1929**, 1096. Selenindigo, p. 61.

3a. CYCLOTELLURIUM COMPOUNDS: *Morgan, Burgess*, J. **1928**, 321. Attempted preparation of tellurindigo: *Mazza, Melchionna*, Rend.accad.sci. Napoli [3a], **34** (1929), 54.

4. PYRROLES*

The ring skeleton of pyrrole, C_4H_5N, is a chain of four carbon atoms closed by a divalent imine group. Being a secondary amine, its basicity is slight; in many of its reactions it resembles phenol. The imine hydrogen is easily replaced by potassium; the potassium salt thus formed reacts with CO_2 or CCl_4 to give pyrrolecarboxylic acids, just as salicylic acid is produced in the *Kolbe* synthesis. Pyrrole aldehydes are also prepared by adaptations of syntheses used for phenol aldehydes. Like the imine hydrogen, the methine hydrogens are very reactive, being readily replaced by various groups and atoms. The constitution of pyrrole and its analogy to furan and thiophene (see page 15) are apparent from its synthesis from γ-dicarbonyl compounds.

This synthesis can be reversed with remarkable smoothness. Hydroxylamine opens the pyrrole ring, producing a dioxime. Pyrrole itself is converted to succindialdoxime (*Ciamician, Zanetti,* Ber. **22,** 1968; *Harries,* Chem.Z. **24,** 857):

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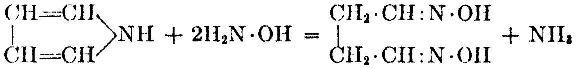
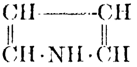
* The chemistry of pyrroles up to the year 1904 has been surveyed by *Ciamician* (Ber. **37**, 4200).



$$\left.\begin{array}{l}CH{=}CH\\ |\\ CH{=}CH\end{array}\right>NH + 2H_2N\cdot OH = \begin{array}{l}CH_2\cdot CH{:}N\cdot OH\\ |\\ CH_2\cdot CH{:}N\cdot OH\end{array} + NH_3$$

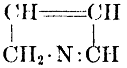
Homologous pyrroles, such as 2-methylpyrrole and 3-isopropylpyrrole, react similarly. This decomposition is useful in determining the position of the alkyl group in homologous pyrroles, since 2-alkylpyrroles give oximes of ketones, while 3-alkylpyrroles are converted to aldoximes, which can be readily oxidized to dibasic acids.

There are several possible formulas for pyrrole, which is not the case for furan or thiophene. The fifth hydrogen could be on the nitrogen (I), on an α-carbon (II) or on a β-carbon (III). The last two formulas are analogous to the methylene form of phenol (IV).



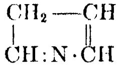
$$\begin{array}{l}CH{-}{-}{-}CH\\ \|\qquad\quad\ \|\\ CH\cdot NH\cdot CH\end{array}$$

Pyrrole
I



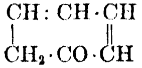
$$\begin{array}{l}CH{=}{=}CH\\ |\qquad\quad |\\ CH_2\cdot N{:}CH\end{array}$$

2-Pyrrolenine
II



$$\begin{array}{l}CH_2{-}{-}CH\\ |\qquad\quad \|\\ CH{:}N\cdot CH\end{array}$$

3-Pyrrolenine
III



$$\begin{array}{l}CH{:}\,CH\cdot CH\\ |\qquad\qquad \|\\ CH_2\cdot CO\cdot CH\end{array}$$

IV

The numbering of the pyrrole ring is similar to that of the furan ring and of the thiophene ring. The numbers 1, 2, 3, 4, and 5, or the symbols α, β, α_1, β_1 are used; in the latter case substituents on the nitrogen are indicated by N—.

While the furan derivatives are important physiologically because of their relation to the carbohydrates, the pyrroles and hydropyrroles are of interest because of their relation to the albumins and to blood pigment, bile pigment, and chlorophyll. Hydrogenated pyrrole rings are also part of the structure of certain alkaloids (nicotine, hygrine, tropine alkaloids).

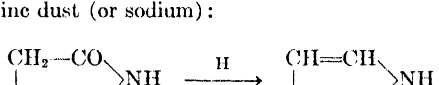
PYRROLE, b.p. 131°, d^{20} 0.9752, received its name from its ability to turn a pine shaving moistened with hydrochloric acid a fiery red (πυῤῥός). It was first found in coal tar and then in bone oil (*Runge,* 1834; *Anderson,* 1858). It is also present in the distillation products of bituminous shales.

Bone oil is still a commercial source of pyrrole and its alkyl derivatives. It is isolated in the form of its potassium salt.

Pyrrole is obtained synthetically (*1*) from ammonium saccharate or mucate by distillation or by heating to 200° in the presence of glycerol (*Khotinsky,* Ber. **42,** 2506); (*2*) by passing acetylene and ammonia through an incandescent tube:

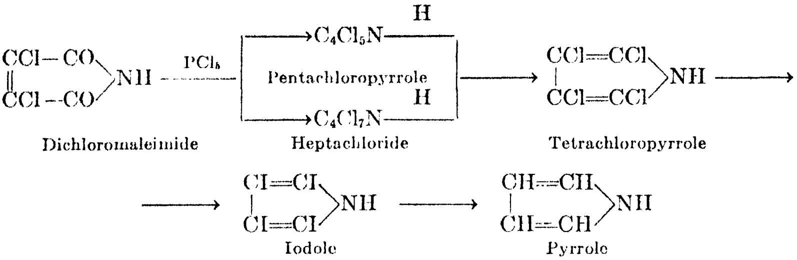
$$2C_2H_2 + NH_3 = C_4H_4NH + H_2$$

(*3*) from various acid imides and lactams, which can also be regarded as oxo derivatives of hydropyrroles (p. 50). Thus, succinimide is reduced to pyrrole by distillation with zinc dust (or sodium):

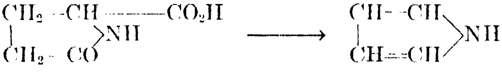


$$\left.\begin{array}{l}CH_2{-}CO\\ |\\ CH_2{-}CO\end{array}\right>NH \xrightarrow{H} \left.\begin{array}{l}CH{=}CH\\ |\\ CH{=}CH\end{array}\right>NH$$

Succinimide and dichloromaleimide, when heated with PCl_5, yield perchlorinated products, which reduce to tetrachloropyrrole. This can be converted through tetraiodopyrrole to pyrrole:



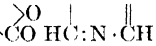
Pyrrole is produced when pyroglutamic acid (Vol. I, p. 613) is heated:



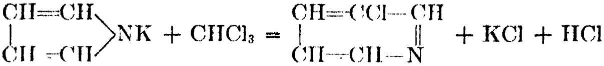
For the ring-synthesis of C-alkyl derivatives, see p. 31.

Pyrrole is a colorless liquid with a characteristic odor. It turns brown on exposure to the air. It is slightly sol. in water and readily sol. in alcohol and ether. It gives an indigo-blue color reaction with *isatin* and *sulfuric acid*, and with *phenanthrenequinone* and other reagents (p. 25) (*Ciamician, Silber*, Ber. **17**, 142; *Meyer, Stadler*, Ber. **17**, 1034; *Ciamician, Magnaghi*, Ber. **19**, 106; *Liebermann, Krauss*, Ber. **40**, 2492). Chromic acid oxidizes pyrrole to maleimide (*Plancher, Cattadori*, Atti accad.Lincei [5] **13**, I, 489). Pyrrole is a very weak base which dissolves slowly in dilute acids; strong acids resinify it rapidly. The solutions in dilute acids when warmed precipitate an amorphous red powder of varying composition, which is called **pyrrole red**. The resinifying action of acids on pyrroles is apparently due to polymerization processes (*Ciamician, Zanetti*, Ber. **26**, 1711). For the isolation and identification of pyrroles the *picrates* or the *mercuric chloride double salts* are used. Pyrrole couples with diazo compounds to give azo dyes.

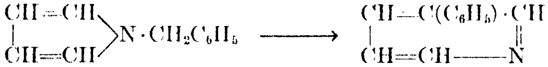
For the qualitative determination of pyrrole and its homologues the color reaction with *Ehrlich's* reagent (4-dimethylaminobenzaldehyde in hydrochloric acid) is usually employed. Pyrroles with a free CH-group give an intensive red coloration in the cold. Tetrasubstituted pyrroles do not react in the cold, but when warmed they generally lose a substituent and give the color reaction. This test is specific for pyrrole only in the absence of a number of other compounds with which dimethylaminobenzaldehyde also gives a color reaction. For the products formed in this reaction, see *Fischer, Nenitzescu*, Z.physiol.Chem. **145**, 295.

3-Phthalidene-3-pyrrolenine (I) (*Dennstedt, Zimmermann*, Ber. **19**, 2201), prepared by warming pyrrole with phthalic anhydride, is probably derived from the desmotropic formula III of pyrrole (p. 29): (I)  . This type of compound is useful for the purification of many pyrrole derivatives.

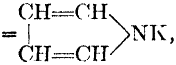
The pyrrole ring can be transformed into a pyridine ring. 3-Chloropyridine is prepared by heating the potassium salt of pyrrole, or pyrrole and sodium alcoholate, with chloroform (for the course of the reaction, see *Ciamician*, Ber. **37**, 4234):



Bromoform gives 3-bromopyridine, methylene iodide gives pyridine (*Dennstedt, Zimmermann*, Ber. **18**, 3316) and benzal chloride gives 3-phenylpyridine. Alkylpyrroles with chloro- and bromoform give homologous 3-chloro- and 3-bromopyridines (*Bocchi*, Gazz. **30**, I, 89). Dichloromethylpyrroles, $(C_4H_3N)CHCl_2$, are probably intermediate products in these reactions. This would also account for the occasional formation of pyrrole aldehydes, which is analogous to the action of chloroform and alkali on phenols (Vol. III, p. 264) (*cf.* the conversion of indoles to quinolines, p. 62). A similar transition of the pyrrole ring to the pyridine ring takes place when vapors of N-alkyl- and 2-alkylpyrroles are passed through an incandescent tube. In this ring enlargement also, the carbon atom entering the ring takes up the 3-position; N-methylpyrrole forms pyridine, N-benzylpyrrole forms 3-phenylpyridine (*Pictet*, Ber. **38**, 1946):



N-*Derivatives of Pyrrole*

The **potassium salt of pyrrole,** C_4H_4NK =  $\begin{matrix} CH{=}CH \\ | \\ CH{=}CH \end{matrix}\!\!>NK$, is formed when metallic potassium is dissolved in pyrrole; hydrogen is evolved, and the salt separates as a crystalline mass. It can also be prepared by heating pyrrole with solid KOH. It hydrolyzes in water to pyrrole and KOH. Sodium reacts much less readily than potassium.

A series of N-derivatives of pyrrole may be prepared from the potassium salt; they are all converted by heat to C-derivatives. The following derivatives are obtained:

With alkyl iodides: **1-alkylpyrroles,** $C_4H_4{:}NR$, which can be prepared directly by using primary amines in place of ammonia in the pyrrole synthesis (p. 15) or by distillation of alkyl- and arylamine salts of mucic acid. **1-Methylpyrrole,** b.p. 113°; **1-ethylpyrrole,** b.p. 131°; **1-isoamylpyrrole,** b.p. 180–184°; **1-phenylpyrrole,** m.p. 62°; **1-(3-pyridyl)pyrrole,** $C_4H_4N \cdot C_5H_4N$, b.p. 251°, from 3-aminopyridine mucate (*Söderbaum*, Ber. 28, 1907).

With acetyl chloride: **1-acetylpyrrole,** oil, b.p. 178°, from pyrrole and acetic anhydride, together with pyrryl methyl ketone (p. 36).

With benzoyl chloride: **1-benzoylpyrrole,** b.p. 276°, which rearranges on heating to 2-pyrryl phenyl ketone (p. 36).

With phosgene: **di-1-pyrryl ketone,** $(C_4H_4N)_2CO$, m.p. 63°, b.p. 238°, which is converted by heat to di-2-pyrryl ketone, $CO(C_4H_3{:}NH)_2$ and 1-(2-pyrroyl) pyrrole.

With chloroformic acid ester: **1-pyrrolecarboxylic acid ester,** $C_4H_4{:}N \cdot CO_2C_2H_5$, b.p. 180°, which forms the **amide,** $C_4H_4{:}N \cdot CO \cdot NH_2$, with ammonia.

With cyanogen chloride: **1-cyanopyrrole,** $C_4H_4N \cdot CN$, which readily polymerizes to a melamine derivative.

Like aniline (Vol. III, p. 78), pyrrole reacts with methylmagnesium iodide to form methane (quantitative determination of NH-groups in pyrroles) and a pyrrylmagnesium iodide, $(C_4H_4N)MgI$, in which the magnesium appears to be attached to the 2-carbon atom, since it yields pyrrole-2-carboxylic acid with CO_2, 2-pyrryl ketones with acid chlorides and fatty acid esters, and bi-2-pyrroyl (p. 36) with oxalyl chloride (*Oddo*, Ber. **43**, 1012; Gazz. **41**, I, 248).

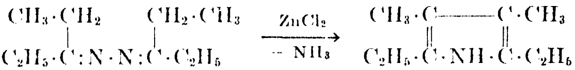
1-Anilinopyrroles, $C_4R_4N \cdot NHC_6H_5$, have been synthesized from 1,4-dioxo compounds with phenylhydrazine (*cf. Smith*, Ann. **289**, 312).

C-*Derivatives of Pyrrole*

1. **C-ALKYLPYRROLES,** homologous pyrroles, occur in bone oil; they are the basic unit of blood and bile pigments and other physiologically important pigments. They are synthesized: (*a*) by passing pyrrole and alcohol vapors over zinc dust; (*b*) by passing 1-alkylpyrroles through an incandescent tube (*Pictet*, Ber. **37, 2792**); (*c*) by heating pyrrole or its potassium salt with alkyl iodides (the N-alkylpyrroles formed first rearrange to C-alkylpyrroles); (*d*) by decarboxylation of alkylpyrrolecarboxylic acids (p. 37); (*e*) by direct synthesis from γ-diketones, such as 2,5-hexanedione (*cf.* p. 15), with ammonia.

(*f*) A series of C-alkylpyrroles have been prepared by reduction of an equimolecular mixture of a ketone and an isonitroso ketone with zinc dust (*Knorr*, Ber. **44**, 2760). The primary products, however, are pyrrole ketones and carboxylic acids, so the method will be discussed in the sections dealing with these compounds.

(*g*) 3,4-Dimethyl-2,5-diethylpyrrole is obtained by a rather unusual synthesis from diethylketazine with $ZnCl_2$ (*Piloty*, Ber. **43**, 493):



$$\begin{matrix} CH_3\cdot CH_2 & & CH_2\cdot CH_3 \\ | & & | \\ C_2H_5\cdot C & :N\cdot N: & C\cdot C_2H_5 \end{matrix} \xrightarrow[-\ NH_3]{ZnCl_2} \begin{matrix} CH_3\cdot C & \text{——} & C\cdot CH_3 \\ \| & & \| \\ C_2H_5\cdot C & \cdot NH\cdot & C\cdot C_2H_5 \end{matrix}$$

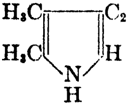
This reaction, which is analogous to the Fischer indole synthesis, is of use only in isolated cases.

(*h*) C-Methyl- and C-ethylpyrroles are prepared by reduction of the corresponding formyl or acetyl compound according to the metod of Wolff-Kishner [*Kishner*, J.Russ.Phys.Chem.Soc. **43** (1911), 582; *Knorr*, *Hess*, Ber. **44**, 2758; *Fischer*, *Bartholomäus*, Ber. **44**, 3314; *Willstätter*, *Asahina*, Ber. **44**, 3707].

(*i*) Methyl groups can be introduced into pyrroles by heating the latter with sodium methylate under pressure; under these conditions 3-ethyl-2,4-dimethylpyrrole (cryptopyrrole) is converted to 3-ethyl-2,4,5-trimethylpyrrole (phyllopyrrole)

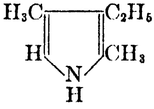
Behavior.—C-Alkylpyrroles are oxidized by fusion with potassium hydroxide to the corresponding pyrrolecarboxylic acids; acid oxidizing agents, such as chromic acid and nitrous acid, sometimes remove alkyl groups in the α-position and give imides of the maleic acid series or their monoximes (*cf.* hemopyrrole) (*Plancher*, *Cattadori*, Atti accad.Lincei [5] **12**, I, 10; *Piloty*, *Quitmann*, Ber. **42**, 4694). Like pyrrole itself, the C-alkyl derivatives are readily resinified by acids.

2-**Methylpyrrole,** b.p. 147°, is prepared from 2-methylpyrrolidine (p. 49) by distillation with zinc dust (*Testoni*, *Mascarelli*, Gazz. **33**, II, 267), from the ethyl ester of 2-methylpyrrole-3-carboxylic acid by saponification and decarboxylation, and from 2-formylpyrrole by reduction with hydrazine and sodium ethylate (*Fischer*, *Beller*, *Stern*, Ber. **61**, 1078). 3-**Methylpyrrole,** b.p. 143° (*Fischer*, *Ernst*, Ann. **447**, 156). 2,3-**Dimethylpyrrole,** b.p. 165°, from 2,3-dimethylpyrrole-4,5-dicarboxylic acid (*Fischer*, *Beller*, *Stern*, Ber. **61**, 1081). 2,5-**Dimethylpyrrole,** b.p. 165°, and 2,4-**dimethylpyrrole,** b.p. 160°, from their dicarboxylic acids (p. 37). 3,4-**Dimethylpyrrole,** m.p. 33°. 2,5-Dimethylpyrrole is opened by nitrous acid to the dioxime of 2,3,4,5-hexanetetrone, $CH_3CO\cdot C(NOH)\cdot C(NOH)\cdot COCH_3$ (*Piloty*, *Quitmann*, Ber. **42**, 4694). 2,4-Dimethylpyrrole is oxidized by chromic acid or nitrous acid to citraconimide or its monoxime (*Plancher*, *Cattadori*, Atti accad.Lincei [5] **12**, I, 10). 4-**Ethyl**-2-**methylpyrrole,** b.p. 86° (20 mm.) (*Fischer*, *Bäumler*, Ann. **468**, 78). 2-**Ethylpyrrole,** b.p. 165°, from 2-acetylpyrrole by the Wolff-Kishner method, and 2-**isopropylpyrrole,** b.p. 175°; they are also formed by the action of acetaldehyde or acetone and zinc chloride on pyrrole. 1,2,5-**Trimethylpyrrole,** b.p. 180°, from its carboxylic acid (*Hinsberg*, Ber. **38**, 1130). 2,3,4-**Trimethylpyrrole,** b.p. 180° (*Fischer*, *Ammann*, Ber. **56**, 2330). 2,5-**Diethyl**-3,4-**dimethylpyrrole,** b.p. 134° (55 mm.). **Tetramethylpyrrole,** m.p. 112° (*Fischer*, *Zerweck*, Ber. **56**, 525; *Fischer*, *Walach*, Ann. **450**, 179).



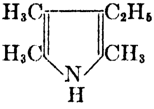
Hemopyrrole

(4-Ethyl-2,3-dimethylpyrrole)
b.p. 88° (12 mm.).
Picrate: m.p. 123°.



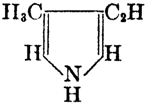
Cryptopyrrole

(3-Ethyl-2,4-dimethylpyrrole)
b.p. 96° (16 mm.).
Picrate: m.p. 140°.



Phyllopyrrole

(4-Ethyl-2,3,5-trimethylpyrrole)
b.p. 90°(10 mm.); m.p., 67°.
Picrate: m.p. 104°.



Opsopyrrole

(4-Ethyl-3-methylpyrrole)
b.p. 75° (13.5 mm.).
No picrate.

The preceding four alkylpyrroles are obtained as cleavage products of physiologically important pigments. *Hemin,* the pigment component of hemoglobin was the first to be split into *alkylpyrroles* and *pyrrolecarboxylic acids* by treatment with boiling HI-glacial acetic acid (*Nencki, Zaleski,* Ber. **34**, 997). The same cleavage products result from the metal-free porphyrins, the bile pigments, and the transformation products of the leaf pigment (chlorophyll).

Hemopyrrole was first obtained in a pure condition as a fission product of hemin (*Fischer, Bartholomäus,* Ber. **44**, 3313). It is synthesized from aminobutanone and acetylpyruvic acid ester (*Piloty, Blömer,* Ber. **45**, 3749) or from 4-isonitroso-3,5-heptanedione and acetoacetic ester (*Fischer, Andersag,* Ann. **450**, 201).

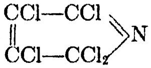
Cryptopyrrole was first isolated in the fission of bilirubin and was later found among the products of the reductive cleavage of blood pigment. It is synthesized from isonitrosoacetone or aminoacetone and acetylacetone, 3-acetyl-2,4-dimethylpyrrole being formed first (*Knorr, Hess,* Ber. **44**, 2758; *Willstätter, Asahina,* Ber. **44**, 3709), or from isonitrosoacetoacetic ester and acetylacetone through 3-acetyl-2,4-dimethylpyrrole-5-carboxylic acid ethyl ester by a Wolff-Kishner reduction (*Fischer, Schubert,* Ber. **56**, 1202; **57**, 612).

Phyllopyrrole was first obtained from chlorophyll and hemin (*Willstätter, Asahina,* Ann. **385**, 188; Ber. **44**, 3707; *Fischer, Bartholomäus,* Ber. **44**, 3313). It is synthesized from cryptopyrrole by heating with sodium methylate in an autoclave (*Fischer, Bartholomäus,* Ber. **45**, 466), or from 3-ethyl-2,4-dimethylpyrrole-5-carboxaldehyde (cryptopyrrolealdehyde, see below) with hydrazine and alcoholate (*Fischer, Schubert,* Ber. **56**, 1209), or from 2,4,5-trimethyl-3-acetylpyrrole with hydrazine and alcoholate (*Fischer, Bartholomäus,* Z. physiol. Chem. **77**, 185).

Opsopyrrole was first described as a fission product of blood pigment (*Piloty, Stock,* Ber. **46**, 1010); this was later confirmed by other investigators (*Fischer, Treibs,* Ann. **450**, 133). It is synthesized from 4-acetyl-3-methylpyrrole (*Fischer, Sturm, Friedrich,* Ann. **461**, 244).

2-**Phenylpyrrole**, m.p. 129°, b.p. 272°, is prepared by the intramolecular rearrangement of 1-phenylpyrrole by heat (*Söderbaum,* Ber. **28**, 1905). 2-**Methyl**-5-**phenylpyrrole**, m.p. 101°. **Tetraphenylpyrrole**, m.p. 211°, from α,α'-dibenzoylbibenzyl and ammonia (*Fehrlin,* Ber. **22**, 553). 2-(2-**Pyridyl**)-**pyrrole**, m.p. 88° (*Tschitschibabin, Bylinkin,* Ber. **56**, 1747). 2-(3-**Pyridyl**)-**pyrrole**, m.p. 72°, is formed by the rearrangement of 1-(3-pyridyl)-pyrrole; the methyl iodide of its N-methyl derivative is identical with the nicotyrine methyl iodide obtained from nicotine (*Söderbaum,* Ber. **28**, 1912).

2. **HALOGEN DERIVATIVES OF PYRROLE.** The halogens react very energetically with pyrroles. To prevent the formation of tar, the halogenation must be done in dilute solution. Even then, all the available hydrogen atoms of the pyrrole nucleus will be immediately replaced. Chlorine and bromine oxidize pyrrole in alkaline solution at once, and convert it to dichloro- or dibromomaleimide.

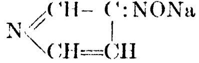
Treatment of pyrrole in ether solution with sulfuryl chloride (1, 2, and 3 mols) gives 2-chloro-, 2,5-dichloro-, and 2,3,5-trichloropyrrole as very unstable liquids; with 4 mols of SO_2Cl_2 tetrachloropyrrole is formed, and further action also replaces the fifth hydrogen atom. This pentachloropyrrole, which can also be obtained from succinimide and dichloromaleimide with PCl_5, is converted to dichloromaleimide by boiling in water; therefore it must be derived from the desmotropic form II of pyrrole (see p. 29), and have the formula  (*Anschütz, Schroeter,* Ann. **295**, 82).

Tetrachloropyrrole, C_4Cl_4NH, m.p. 110° (dec.), sublimable, white needles, which turn black after a short time due to spontaneous decomposition. Potassium iodide converts it to iodole (see below).

Pentachloropyrrole, C_4Cl_5N, yellowish oil, b.p. 209°, b.p. 90.5° (10 mm.), gives a heptachloride when heated with PCl_5; both of these compounds can be reduced to tetrachloropyrrole.

Tetraiodopyrrole, iodole, $C_4I_4{:}NH$, yellowish brown prisms, m.p. 140° (dec.), is best prepared by treating pyrrole with iodine in the presence of alkali. Tetraiodopyrrole is odorless; it is used as an *antiseptic,* having the same action as iodoform.

3. **NITROSO- AND NITROPYRROLES.** Since pyrrole and its homologues are resinified by acids, these compounds must be obtained indirectly, and are easily decomposed. On the other hand, in many cases *acetyl* and *carboxyl* groups, and sometimes methyl groups, can be smoothly replaced by NO_2 (*Fischer, Zerweck,* Ber. **55,** 1949). Pyrrole and its homologues with a free methine group in the β-position react with amyl nitrite and sodium ethylate to form sodium salts of 3-isonitrosopyrroles:



$$N\begin{matrix}\diagup CH-C:NONa\\ \qquad\qquad | \\ \diagdown CH=CH\qquad\end{matrix}$$

, which are derived from the desmotropic formula III of pyrrole (p. 29).

For the sodium salts of **isonitrosopyrrole,** 2,4- and **2,5-dimethyl-3-isonitrosopyrrole,** see *Angeli, Angelico, Calvello,* Atti accad.Lincei [5] **11,** II, 16; *Angelico, ibid.* [5] **14,** I, 699; *Angelico, Calvello,* Gazz. **34,** I, 38. 2,5-Dimethyl-3-isonitrosopyrrole is converted by hydroxylamine to the trioxime of 2,3,5-hexanetrione, $CH_3CO\cdot CO\cdot CH_2\cdot COCH_3$ (*cf.* p. 29).

3-Nitropyrrole, $(C_4H_4N)NO_2$, bright yellow rhombohedrons, m.p. 63°; its sodium salt, $(C_4H_3N):NOONa$, is prepared from pyrrole and ethyl nitrate in the presence of sodium ethylate. **Nitro-2,4-dimethylpyrrole,** m.p. 111° (*Angeli, Alessandri,* Atti accad.Lincei [5] **20,** I, 311).

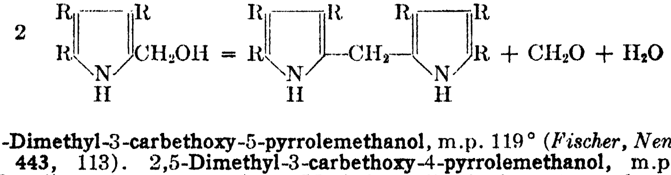
Dinitropyrrole, m.p. 152°, is prepared from pyrryl methyl ketone. **3,4-Dinitropyrrole,** m.p. 101° (*Hale, Hoyt,* Am. **37,** 2538). **2,4-Dimethyl-5-nitropyrrole-3-carboxylic acid ethyl ester,** m.p. 149°, from the corresponding 5-acetylpyrrole and HNO_3 ($d = 1.4$); **2,4-dimethyl-3-nitropyrrole-5-carboxylic acid ethyl ester,** m.p. 204°, is prepared in the same way; **2,4-dinitropyrrole-3,5-dicarboxylic acid ethyl ester,** m.p. 136°, from 2,4-dimethylpyrrole-3,5-dicarboxylic acid ethyl ester by removal of the two methyl groups (*Fischer, Zerweck,* Ber. **55,** 1954).

4. **AMINOPYRROLES.** 3-*Aminopyrroles* are relatively easy to obtain by reduction of the corresponding nitropyrroles with Al-amalgam in ether containing water (*Fischer, Stern,* Ann. **446,** 229). 2-*Aminopyrroles* may possibly be present in the reduction products of 2-*pyrroleazo compounds* (*Fischer, Rothweiler,* Ber. **56,** 512).

5. **PYRROLEAZO COMPOUNDS.** Benzenediazonium salts couple with pyrrole and its homologues to give **monoazo** and **diazo** compounds, which are analogous to the azo dyestuffs of the benzene series (*Fischer, Hepp,* Ber. **19,** 2251). The affinity of the pyrroles for diazo compounds is sometimes so great that carboxyl groups in the 2-position are displaced by the azo radical (*Fischer, Rothweiler,* Ber. **56,** 513). The reaction is often used for the identification of pyrroles with free CH-groups, with diazobenzenesulfonic acid as the diazo component. It can also serve to separate tri- and tetra-substituted pyrroles, since the latter do not couple.

6. **PYRROLEMETHANOLS** are prepared by reduction of the easily obtained *pyrrolecarboxaldehydes* with aluminum amalgam (*Fischer, Stern,* Ann. **446,** 229); aldol condensation of pyrroles having a free 2-position with formaldehyde in an alkaline medium yields 2-*pyrrolemethanols* [*Tschelinzev, Maxorov,* J.Russ.Phys. Chem.Soc. **48** (1916), 748; *Fischer, Nenitzescu,* Ann. **443,** 113].

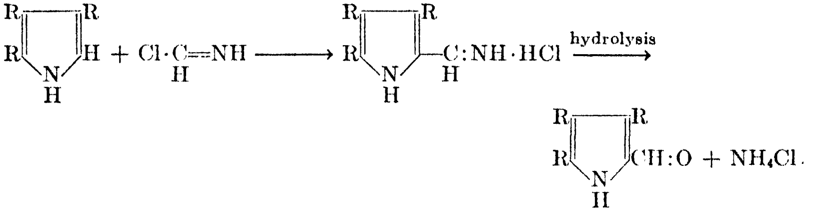
Methanol groups in the 2-position are remarkably active. On storing or heating, 2-pyrrolemethanols either split into formaldehyde and a pyrrole with a free methine group, or undergo a bimolecular condensation to form a dipyrrylmethane (*Fischer, Nenitzescu,* Ann. **443,** 113):



2,4-Dimethyl-3-carbethoxy-5-pyrrolemethanol, m.p. 119° (*Fischer, Nenitzescu,* Ann. **443,** 113). **2,5-Dimethyl-3-carbethoxy-4-pyrrolemethanol,** m.p. 131° (*Fischer, Stern,* Ann. **446,** 234). **2-Methyl-3,5-dicarbethoxy-4-pyrrolemethanol,** m.p. 132° (*Fischer, Treibs,* Ann. **457,** 246). **2,5-Pyrroledimethanol,** $(C_4H_2NH)(CH_2OH)_2$: *Tschelinzev, Maxorov,* J.Russ.Phys.Chem.Soc. **48** (1916), 748.

7. **PYRROLECARBOXALDEHYDES.** This class of compounds serves as starting material in the synthesis of the acid cleavage products of blood pigment,

and a good method of preparation is, therefore, highly important. The reaction analogous to the *Reimer-Tiemann* synthesis for aromatic hydroxyaldehydes ($CHCl_3 + KOH$) gives rather low yields. The best method consists in the treatment of an ether or chloroform solution of the pyrrole with hydrocyanic acid and hydrochloric acid (*Fischer, Zerweck*, Ber. **55**, 1946). Probably formimide chloride is formed as an intermediate product.



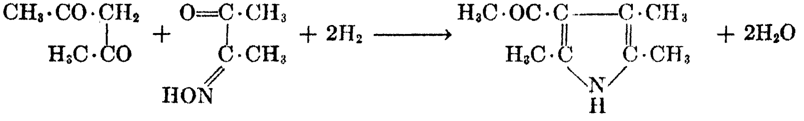
(For another synthesis of pyrrolecarboxaldehydes, see *Fischer, Ernst*, Ann. **447**, 140.)

Properties.—The pyrrolecarboxaldehydes behave in many respects like other aldehydes, oxidizing to the corresponding acid, forming oximes and phenylhydrazones, *etc.* They do not, however, give the *Angeli-Rimini* reaction (Vol. I, p. 130), or give a color with fuchsinsulfurous acid. The aldehyde group is reduced to a methyl group by hydrazine hydrate and sodium ethylate. The most significant reactions of these compounds are the formation of dipyrrylmethenes and the condensation of the aldehyde group with reactive CH_2-groups.

2-**Pyrrolecarboxaldehyde,** m.p. 45° (*Bamberger, Djierdjian*, Ber. **33**, 536; *Fischer, Beller, Stern*, Ber. **61**, 1078); 2,4-**dimethyl-5-pyrrolecarboxaldehyde,** m.p. 90° (*Fischer, Nenitzescu*, Ann. **443**, 128); 2,4-**dimethyl-3-ethyl-5-pyrrolecarboxaldehyde** (*cryptopyrrolecarboxaldehyde*), m.p. 106° (*Fischer, Schubert*, Ber. **56**, 1209); 2,3-**dimethyl-4-ethyl-5-pyrrolecarboxaldehyde** (*hemopyrrolecarboxaldehyde*), m.p. 155° (*Fischer, Stangler*, Ann. **459**, 98); 2,4-**dimethyl-5-formylpyrrole-3-carboxylic acid ethyl ester,** m.p. 165° (*Fischer, Zerweck*, Ber. **55**, 1946); 2,5-**dimethyl-4-formylpyrrole-3-carboxylic acid ethyl ester,** m.p. 151° (*ibid.*, 1948); 2,4,5-**trimethylpyrrole-3-carboxaldehyde,** m.p. 141° (*Fischer, Zerweck*, Ber. **56**, 521); 2,4-**dimethyl-3-formylpyrrole-5-carboxylic acid ethyl ester,** m.p. 145° (*Fischer, Weiss, Schubert*, Ber. **56**, 1200); 5-**formyl-4-methyl-3-pyrrolepropionic acid** (*formylopsopyrrolecarboxylic acid*), m.p. 152° (*Fischer, Treibs*, Ber. **60**, 379); 4,5-**dimethyl-2-formyl-3-pyrrolepropionic acid** (*formylhemopyrrolecarboxylic acid*), m.p. 155° (*Fischer, Platz, Morgenroth*, Z.physiol.Chem. **182**, 280); 2,4-**dimethyl-5-formyl-3-pyrrolepropionic acid** (*formylcryptopyrrolecarboxylic acid*), m.p. 151° (*Fischer, Schubert*, Ber. **57**, 615).

8. **PYRRYL KETONES** are prepared: (*a*) by heating pyrrole with acid anhydrides, together with N-acylpyrroles (p. 31), from which the ketones can also be obtained by an intramolecular rearrangement; (*b*) by treatment of pyrrylmagnesium iodide (p. 31, and *Oddo*, Ber. **43**, 1012) with acid chlorides or fatty acid esters (*Tschelinzev, Terentjev*, Ber. **47**, 2647); (*c*) by the action of nitriles and hydrochloric acid on pyrroles, analogous to the formation of aldehydes; (*d*) by application of the Friedel-Crafts synthesis (*Fischer*, Z.physiol.Chem. **155**, 99).

In addition to these methods of preparation, in which an acyl radical is introduced into a pyrrole having a free CH-group, pyrryl ketones can also be obtained by direct ring-synthesis. The most important method consists in the reduction of a mixture of an *isonitroso ketone* and a 1,3-*diketone* in acetic acid solution with zinc dust (*Knorr*, Ber. **44**, 2760). From acetylacetone and isonitrosoethyl methyl ketone, 3-*acetyl*-2,4,5-*trimethylpyrrole* is formed:



The principal application of this type of synthesis is in the preparation of *pyrrolecarboxylic acids* (see below).

Properties.—C-Acetylpyrroles are oxidized by potassium permanganate to pyrroleglyoxylic acids, which are converted to pyrrolecarboxylic acids by alkali fusion. Higher acyl radicals, from propionyl up, are often split off by the action of H_2SO_4 (*Fischer, Andersag,* Ann. **450,** 201). With benzaldehyde they condense to characteristic styryl pyrryl ketones, such as $C_4H_3NH \cdot COCH{:}CHC_6H_5$.

Methyl 2-pyrryl ketone, 2-*acetylpyrrole,* m.p. 90°. **Ethyl 2-pyrryl ketone,** m.p. 52.5°. **Propyl 2-pyrryl ketone,** m.p. 48.5°. **Phenyl 2-pyrryl ketone,** 2-*benzoylpyrrole,* m.p. 78°. **Benzyl 2-pyrryl ketone,** m.p. 95° (for all these ketones, see *Oddo,* Ber. **43,** 1014). **Di-2-pyrryl ketone,** 2-(2-*pyrroyl*)*pyrrole,* m.p. 160°, is formed together with 1-(2-*pyrroyl*)*pyrrole,* m.p. 63°, by heating 1,1′-carbonyldipyrrole (*Ciamician, Magnaghi,* Ber. **18,** 419, 1829). **3,5-Dimethyl-4-acetylpyrrole-2-carboxylic acid ethyl ester,** m.p. 143° (*Zanetti, Levi,* Gazz., **24,** I, 547).

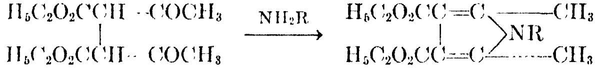
Bi-2-pyrroyl, yellow, m.p. 200°, from pyrrylmagnesium iodide and oxalyl chloride. 2,5-**Diacetylpyrrole,** m.p. 162°.

9. **PYRROLECARBOXYLIC ACIDS.** The pyrrolecarboxylic acids resemble the hydroxybenzoic acids and are produced by similar reactions: (*a*) oxidation of homologous pyrroles by fusion with alkali; (*b*) treatment of the potassium salt of pyrrole with CO_2:

$$C_4H_4NK + CO_2 = C_4H_3(CO_2K)NH$$

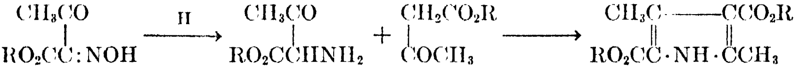
(*c*) reaction of pyrrylmagnesium compounds with chloroformic acid ester.

The esters of homologous pyrrolecarboxylic acids are obtained by ring-synthesis: (*d*) from γ-dioxomonocarboxylic and -dicarboxylic acid esters with alcoholic ammonia; instead of ammonia, primary amines, amino acids, hydroxylamines, or phenylhydrazines can be used:



$$\begin{matrix} H_5C_2O_2CCH-COCH_3 \\ | \\ H_5C_2O_2CCH-COCH_3 \end{matrix} \xrightarrow{NH_2R} \begin{matrix} H_5C_2O_2CC=C-CH_3 \\ | \quad\quad > NR \\ H_5C_2O_2CC=C-CH_3 \end{matrix}$$

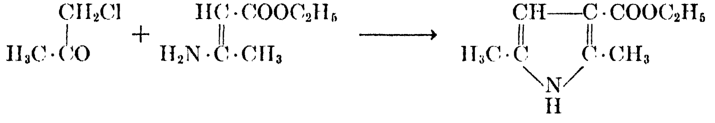
(*e*) By reduction of an equimolar mixture of isonitrosoacetoacetic ester and acetoacetic ester (*Knorr*):



$$\begin{matrix} CH_3CO \\ | \\ RO_2CC{:}NOH \end{matrix} \xrightarrow{H} \begin{matrix} CH_3CO \\ | \\ RO_2CCHNH_2 \end{matrix} + \begin{matrix} CH_2CO_2R \\ | \\ COCH_3 \end{matrix} \longrightarrow \begin{matrix} CH_3C-CCO_2R \\ \| \quad\quad \| \\ RO_2CC\cdot NH\cdot CCH_3 \end{matrix}$$

The last step in this synthesis is the reaction between the amino ketone, formed in the first part of the synthesis, and the second component, which can be a ketone (p. **32**), an oxocarboxylic acid ester, or a 1,3-diketone (p. **31**). Its wide range of application makes it one of the most important methods for the preparation of pyrroles.

(*f*) Closely related to the above synthesis is the formation of pyrroles by the reaction of chloro ketones and acetoacetic ester with ammonia. This rather unusual synthesis yields β-aminocrotonic acid ester as an intermediate product (*Hantzsch,* Ber. **23,** 1474; *Korschun,* Ber. **38,** 1125; *Benary,* Ber. **44,** 493). Furan derivatives are obtained as side-products.



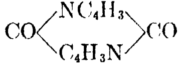
$$\begin{matrix} CH_2Cl \\ | \\ H_3C\cdot CO \end{matrix} + \begin{matrix} HC\cdot COOC_2H_5 \\ \| \\ H_2N\cdot C\cdot CH_3 \end{matrix} \longrightarrow \begin{matrix} CH-C\cdot COOC_2H_5 \\ \| \quad\quad \| \\ H_3C\cdot C \quad C\cdot CH_3 \\ \diagdown \; \diagup \\ N \\ H \end{matrix}$$

A large number of pyrroles can be prepared by this reaction, using as starting materials various chloro ketones, chloro-oxo-carboxylic acids and chloroacetaldehyde, which reacts as the asym. dichloro ether (*Natterer,* Mo. **5,** 491). Hydroxy ketones can be used in place of chloro ketones.

Properties.—In the saponification of pyrrolepolycarboxylic acid esters, carbethoxy groups in the 2-position are attacked first, which makes possible the preparation of ester-carboxylic acids. With concentrated sulfuric acid, however, the 4-carbethoxy group in 3,5-dimethylpyrrole-2,4-dicarboxylic acid ethyl ester is saponified first (*Fischer, Walach,* Ber. **58**, 2820). Pyrrolecarboxylic acids are decarboxylated on heating, leaving the corresponding pyrroles. Pyrrolecarboxylic acids are readily converted by loss of water to dimolecular anhydrides, which are called *pyrocolls* because they are also obtained in the distillation of glue (χόλλα).

(*a*) *Carboxylic acids with the carboxyl group on the nucleus.*

2-Pyrrolecarboxylic acid, m.p. 192° (dec. 207°) (*Bamberger, Djierdjian,* Ber. **33**, 541) is obtained in the form of its amide, m.p. 176°, together with pyrrole, by heating ammonium mucate. Chloride, m.p. 110°; hydrazide, m.p. 232°; azide, $C_4H_3NH \cdot CON_3$, converted to 2-pyrrolecarbamic acid ethyl ester, $(C_4H_3NH)NH \cdot CO_2C_2H_5$, m.p. 56°, by boiling with alcohol.

Pyrocoll,  $CO\left\langle\begin{matrix}NC_4H_3\\C_4H_3N\end{matrix}\right\rangle CO$, m.p. 268°, is produced in the distillation of glue, and is prepared by warming 2-pyrrolecarboxylic acid with acetic anhydride.

3-Pyrrolecarboxylic acid, m.p. 162°, is prepared by treating the potassium salt of pyrrole with CO_2 at 200° or pyrrylmagnesium bromide with CO_2 at 250°, or by fusing 3-methylpyrrole with potassium hydroxide.

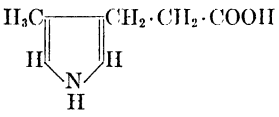
2,5-Pyrroledicarboxylic acid turns black at 260°.

2-Methylpyrrole-3-carboxylic acid, m.p. 169°. **4-Methylpyrrole-3-carboxylic acid,** m.p. 149°. **4,5-Dimethylpyrrole-3-carboxylic acid,** m.p. 188°, from the dicarboxylic acid by decarboxylation. **2,5-Dimethylpyrrole-3,4-dicarboxylic acid,** m.p. 250°; its diethyl ester is formed by the action of ammonia on diacetylsuccinic acid ester. **2,4-Dimethylpyrrole-3-carboxylic acid,** m.p. 183° (*Piloty, Hirsch,* Ann. **395**, 70), and **3,5-dimethylpyrrole-2-carboxylic acid,** m.p. 136° (*Fischer, Weiss, Schubert,* Ber. **56**, 1199), both from 3,5-dimethylpyrrole-2,4-dicarboxylic acid ester, m.p. 136° (*Knorr, Hess,* Ber. **45**, 2629). **3,5-Dimethyl-4-vinylpyrrole-2-carboxylic acid,** m.p. 102° (*Fischer, Walach,* Ber. **58**, 2821).

(*b*) *Carboxylic acids with the carboxyl group in the side-chain.*

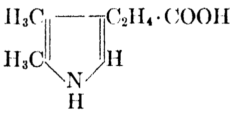
3,5-Dicarboxy-2,4-pyrrolediacetic acid, m.p. 220° (dec.), from the *tetraethyl ester,* m.p. 113° (*Feist,* Ber. **35**, 1557).

Several acids of this type, having a propionic acid residue in the 3-position, are cleavage products of the blood, bile, and plant pigments (p. 41 and Vol. I, p. 751). The following four acids, which are carboxylic acid derivatives of the homologous pyrroles described on p. 32, have been so obtained:



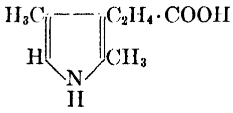
Opsopyrrolecarboxylic acid

4-Methyl-3-pyrrolepropionic acid, m.p. 119° (*Bergmann, et al.,* Ann. **450**, 144). Prep. from cryptopyrrolecarboxylic acid: *Fischer, Lamatsch,* Ann. **462**, 240.



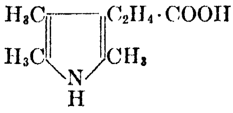
Hemopyrrolecarboxylic acid

4,5-Dimethyl-3-pyrrolepropionic acid, m.p. 130°; picrate m.p. 163° (*Piloty,* Ann. **366**, 237; *Piloty, et al.,* Ann. **406**, 342). Synthesis: *Fischer, Treibs,* Ber. **60**, 379; *Fischer, Lamatsch,* Ann. **462**, 248.



Cryptopyrrolecarboxylic acid

2,4-Dimethyl-3-pyrrolepropionic acid, m.p. 141°; picrate, m.p. 156° (*Piloty, Thannhauser,* Ann. **390**, 191; *Fischer, Röse,* Ber. **47**, 792). Synthesis: *Fischer, Weiss,* Ber. **57**, 602.



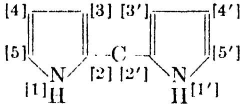
Phyllopyrrolecarboxylic acid

2,4,5-Trimethyl-3-pyrrolepropionic acid, m.p. 88°; picrate, m.p. 124° (*Piloty, Dormann,* Ber. **46**, 1007). Synthesis: *Fischer, Nenitzescu,* Ann. **439**, 175.

Xanthopyrrolecarboxylic acid, *2-ethyl-4-methyl-3-pyrrolepropionic acid,* m.p. 126°, had been assumed for some time to be a cleavage product of blood pigment (*Piloty, Stock, Dormann,* Ann. **406,** 343); more recent experimental results disprove this. Synthesis: *Fischer, Klarer,* Ann. **447,** 62.

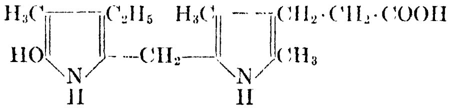
Compounds Containing Pyrrole Rings Joined by $-CH_2$ or $=CH$

Compounds of this class have a special significance because of their relation to blood pigment. Hemin, the pigment component obtained from hemoglobin with glacial acetic acid-hydrochloric acid, decomposes on total reductive degradation into basic and acid pyrrole fragments, whose sum always indicates the presence of four pyrrole nuclei in the hemin molecule (p. 33, and Vol. I, p. 750). The presence of a methyl group in the 2-position in most of the pyrrole fragments suggested that a linkage of this type:



held the pyrrole nuclei together in the hemin molecule. This conception, together with the analytical results and the oxidative degradation (hematinic acid, Vol. I, p. 750), led to the first formulation of a structure for hemin [*Küster,* Ber. deut.pharm.Ges. **21** (1912), 513].

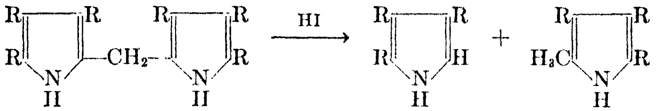
This linkage was verified experimentally by the isolation of *bilirubic acid* from bile pigment, which is closely related to blood pigment, simultaneously by *H. Fischer* and *Röse* (Z.physiol.Chem. **89,** 256; Ber. **45,** 1581) and by *Piloty* and *Thannhauser* (Ann. **390,** 191). Bilirubic acid was proved by *Fischer* to be a dipyrrylmethane derivative with this formula:



The dipyrrylmethanes (methylenedipyrroles) and their dehydrogenation products, the dipyrrylmethenes (pyrrylmethylenepyrrolenines) have therefore been the subject of many investigations.

Preparation.—The dipyrrylmethanes were first synthesized by the condensation of benzaldehyde with pyrroles having a free methine group in the presence of potassium bisulfate (*Feist,* Ber. **35,** 1647); later they were obtained from formaldehyde, pyrroles, and alcoholic hydrochloric acid (*Colacicchi,* Atti accad.Lincei [5] **20,** II, 312; *Fischer, Bartholomäus,* Z.physiol.Chem. **83,** 50). 2-Pyrrylmethanols readily split off formaldehyde to form dipyrrylmethanes (*Fischer, Nenitzescu,* Ann. **443,** 113). A similar reaction converts 2-bromomethylpyrroles to dipyrrylmethanes (*Fischer, Walach,* Ann. **450,** 111).

Properties.—The colorless dipyrrylmethanes are split at the methane linkage by HI-glacial acetic acid, the methyl group being left at the 2-position of one pyrrole nucleus and a hydrogen at the 2-position of the other:



For the conversion into dipyrrylmethenes with oxidizing agents, see below.

3,5,3′,5′-**Tetramethyl-2,2′-pyrromethane**, 2,2′-*methylene-bis-(3,5-dimethylpyrrole)*, m.p. 140° (*Fischer, Bartholomäus*, Z.physiol.Chem. **83**, 51).

4,4′-Dimethyl-5,5′-dicarboxy-2,2′-pyrromethane-3,3′-dipropionic acid, m.p. 176° (dec.) (*Fischer, Andersag*, Ann. **450**, 217).

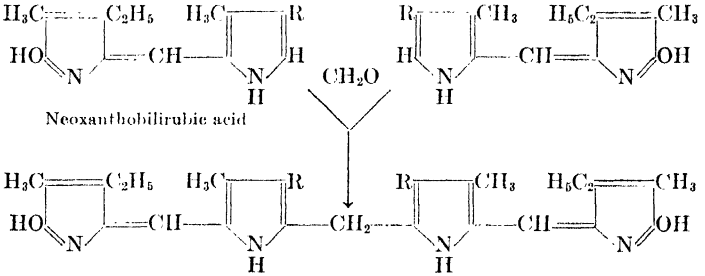
3,3′-Dimethyl-4,4′-diethyl-5,5′-dicarboxy-2,2′-pyrromethane, m.p. 211°.

3,5,3′,5′-Tetramethyl-2,2′-pyrromethane-4,4′-dicarboxylic acid diethyl ester, m.p. 223° (*Fischer, Röse*, Ber. **47**, 792).

3,5,3′,5′-Tetramethyl-2,2′-pyrro-phenylmethane-4,4′-dicarboxylic acid diethyl ester, m.p. 188° (*Feist*, Ber. **35**, 1653).

Bilirubic acid, m.p. 187° (formula shown on p. 38), is formed when bilirubin is split in two by the action of HI-glacial acetic acid. On oxidation it is converted to methylethylmaleimide and hematinic acid (*Knorr, Hess*, Ber. **45**, 1579). Milder oxidation gives the yellow **xanthobilirubic acid,** m.p. 274° (*Fischer, Röse*, Ber. **46**, 440), which can also be obtained directly from mesobilirubinogen (Vol. I, p. 753) by treatment with potassium methylate (*Fischer, Röse*, Z.physiol. Chem. **89**, 260). The xanthobilirubic acid is converted back to bilirubic acid by sodium amalgam. Very energetic treatment with glacial acetic acid and potassium iodide splits bilirubic acid into cryptopyrrole and cryptopyrrolecarboxylic acid (*Fischer, Röse*, Ber. **45**, 3274). Heating with potassium methylate removes only the acid component, as phyllopyrrolecarboxylic acid (*Fischer, Röse*, Z.physiol.Chem. **89**, 260).

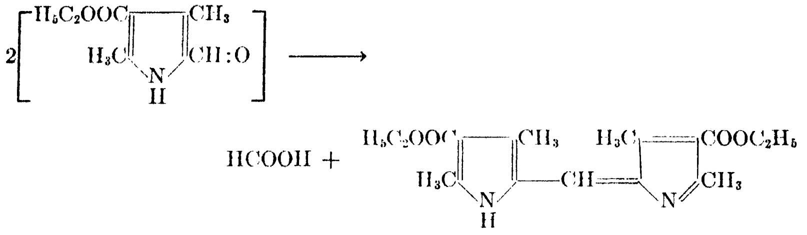
Neobilirubic acid, m.p. 187°, is obtained, together with bilirubic acid, by treatment of mesobilirubin with HI-glacial acetic acid, and also from neoxanthobilirubic acid by reduction with sodium amalgam. Its formula is the same as that of bilirubic acid, but with the 2-methyl group replaced by a free :CH-group. Its constitution is shown by the formation of hemopyrrolecarboxylic acid (p. 37) on reductive degradation with hydrogen iodide. Mild oxidation with potassium methylate gives **neoxanthobilirubic acid,** m.p. 227°, which is also obtained by the fusion of mesobilirubin with resorcinol. Mesobilirubin (Vol. I, p. 753) can be synthesized by the condensation of this acid with formaldehyde:



Mesobilirubin
(R = $CH_2 \cdot CH_2 \cdot COOH$)

These reactions also determine the fundamental structure of bilirubin (bile pigment), the important regenerative component of blood pigment; its constitution has been further verified by partial synthesis (*Fischer, Hess*, Z.physiol.Chem. **194**, 193).

DIPYRRYLMETHENES, *pyrrylmethylenepyrrolenines*, contain two pyrrole nuclei joined by a methine linkage, usually in the 2-positions. They are prepared: (*1*) By mild oxidation (ferric chloride) of dipyrrylmethanes in acid solution (*Piloty, Krannich, Will*, Ber. **47**, 2544). (*2*) From two mols of pyrrolecarboxaldehyde by splitting off of formic acid (*Fischer, Zerweck*, Ber. **55**, 1942):



The production of dipyrrylmethenes from pyrrolecarboxaldehydes and trisubstituted pyrroles or pyrrolecarboxylic acids, such as crypto- or hemopyrrolecarboxylic acid, is particularly important. For the preparation of unsymmetrical methenes, see *Fischer, Schubert*, Ber. **56**, 1204. (*3*) By direct condensation of trisubstituted pyrroles with concentrated formic acid and 48% HBr; this reaction is also possible with tetrasubstituted pyrroles if the 2-position is occupied by —COOH or —$COOC_2H_5$ (*Fischer, Friedrich, Lamatsch, Morgenroth*, Ann. **466**, 165). (*4*) By the action of excess bromine on certain 2-methylpyrroles, such as cryptopyrrole.

The highly colored dipyrrylmethenes form salts with mineral acids, and characteristic complex salts with iron, copper, magnesium, etc. (*Fischer, Schubert*, Ber. **56**, 1205; *Fischer, Ammann*, Ber. **56**, 2324).

3,3′-Diethyl-4,4′,5,5′-tetramethyl-2,2′-pyrromethene, 2-(*4,5-dimethyl-3-ethyl-2-pyrrylmethylene*)-*4,5-dimethyl-3-ethylpyrrolenine*), m.p. 108° (*Piloty, Stock, Dormann*, Ber. **47**, 400; *Fischer, Schubert*, Ber. **57**, 614). **3,3′,5,5′-Tetramethyl-2,2′-pyrromethene**, m.p. 117° (*Fischer, Weiss, Schubert*, Ber. **56**, 1199). **4,4′-Dicarbethoxy-3,3′,5,5′-tetramethyl-2,2′-pyrromethene**, red needles, m.p. 190° (*Fischer, Zerweck*, Ber. **56**, 526). **4,4′-Diethyl-3,3′,5,5′-tetramethyl-2,2′-pyrromethene**, perchlorate, red needles, dec. 240° (*Fischer, Schubert*, Ber. **56**, 1210).

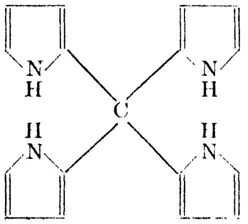
TRIPYRRYLMETHANES (*methylidynetripyrroles*) are produced by the action of chloroform and KOH on trisubstituted pyrroles (*Fischer, Ammann*, Ber. **56**, 2319). A better method is the condensation of trisubstituted pyrroles with pyrrole aldehydes in the presence of potassium bisulfate (*Fischer, Ammann*, Ber. **56**, 2319; *Fischer, Heyse*, Ann. **439**, 246).

The tripyrrylmethanes are colorless. They are split by concentrated hydrochloric acid into dipyrrylmethanes and trisubstituted pyrroles.

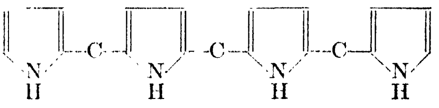
5,5′,5″-Methylidynetris-[3-acetyl-2,4-dimethylpyrrole], **tris(4-acetyl-3,5-dimethyl-2-pyrryl)methane**, colorless prisms, m.p. 265° (*Fischer, Ammann*, Ber. **56**, 2325).

5,5′,5″-Methylidynetris-[2,4-dimethyl-3-pyrrolecarboxylic acid] triethyl ester, tris(4-carbethoxy-3,5-dimethyl-2-pyrryl)methane, m.p. 194°.

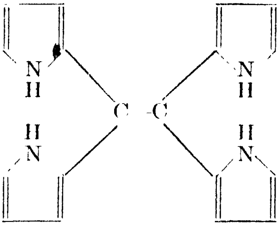
Compounds containing four pyrrole nuclei are of particular interest, since hemin is of this type. The following diagrams indicate schematically four possible structures for such compounds, in which the nuclei are always joined at the 2-position:



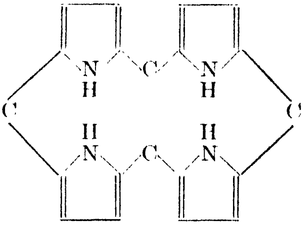
I. Tetrapyrrylmethane type



II. Linear chain of four pyrroles



III. Tetrapyrrylethane type



IV. Type II closed to a ring

No tetrapyrrylmethanes are yet known. A compound of type II has been reported by *Fischer* and *Scheyer* (Ann. **434,** 237), and is also present in mesobilirubin (p. 39).

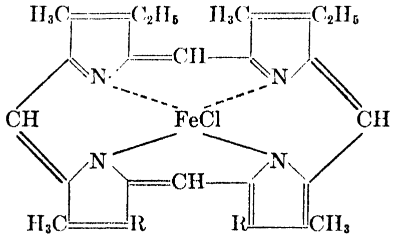
The **tetrapyrrylethane** structure is of greater significance than the first two, since it has been assumed to be the skeleton for etioporphyrin by *Willstätter* (1913) (see *Untersuchungen uber Chlorophyll*, p. 39, and Ber. **56,** 2380), and for the blood and bile pigments by *H. Fischer* (Z.physiol.Chem. **89,** 261, 263). The correctness of these assumptions was tested by synthesis of this type of tetrapyrrylethanes and -ethylenes.

Preparation.—Tetrapyrrylethanes are obtained by the reaction of trisubstituted pyrroles with glyoxal or glyoxal sulfate (Vol. I, p. 398) in the presence of dehydrating agents (*Fischer, Eismayer*, Ber. **47,** 2019; *Fischer, Schubert*, Ber. **56,** 2379; *Fischer, Beller*, Ann. **444,** 238).

If the formulas proposed by *Willstätter* and by *Fischer* for the physiologically important pigments were correct, then their leuco derivatives should resemble the synthesized tetrapyrrylethanes. They do not. Attempts to dehydrogenate tetrapyrrylethanes in acid solution often cause fracture of the molecule to dipyrrylmethenes (*Fischer, Schubert*, Ber. **56,** 2379). HI-glacial acetic acid also breaks the ethane linkage, with formation of monocyclic pyrroles. Only in a few cases does dehydrogenation remove two hydrogen atoms from the ethane bridge to leave yellow tetrapyrrylethylenes (*Fischer, Beller*, Ann. **444,** 238).

Tetrakis-(3-carbethoxy-2,4-dimethyl-5-pyrryl)-ethane, colorless platelets, m.p. 282°.

The fourth type of structure shown above has been proposed by *Küster* [Ber.deut.pharm.Ges. **21** (1912), 513] as the formula for hemin. In the following formula, $R = -CH_2 \cdot CH_2 \cdot COOH$.

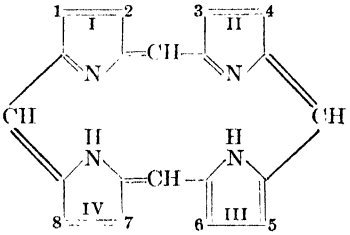


Hemin (according to *Küster*, but with the substituents correctly placed)

This formula is essentially a cyclic pyrrole complex with methine bridges between the 2-carbon atoms. It takes into account the results obtained by analysis and by oxidative and reductive degradation of hemin.

Subsequent investigation of the structure of the blood pigment has shown that *Küster's* formula is basically correct. A conclusive proof, as in many other cases, can be obtained only by synthesis. As a foundation for such a synthesis, a broad development of the chemistry of simple pyrroles was necessary; this was provided in the work of *H. Fischer*, particularly in the synthesis of the acid components of the blood pigment.

Elimination of iron from hemin leaves metal-free compounds, which are called porphyrins (πορφυρ purple). By removal of the side-chains the tetracyclic parent compound, porphine, is obtained (see Vol. I, p. 751).



Porphine nucleus

Porphyrins are prepared from this parent compound by the introduction of substituents in the β-positions, which are numbered from 1 to 8. Alkyl groups in these positions give basic porphyrins, and alternate alkyl and propionic acid or methylmalonic acid groups give acid porphyrins. Some porphyrins contain free methine groups (deuteroporphyrins). Hemins are obtained by introducing iron into porphyrins, and phyllins, by introducing magnesium. It is apparent from the formula of the porphine nucleus that there are four isomers possible for a tetramethyltetraethylporphyrin (an etioporphyrin), if each ring is substituted by one methyl and one ethyl group:

Etioporphyrin I: 1,3,5,7-tetramethyl-2,4,6,8-tetraethylporphine
" II: 1,4,5,8- " -2,3,6,7- "
" III: 1,3,5,8- " -2,4,6,7- "
" IV: 1,4,6,7- " -2,3,5,8- "

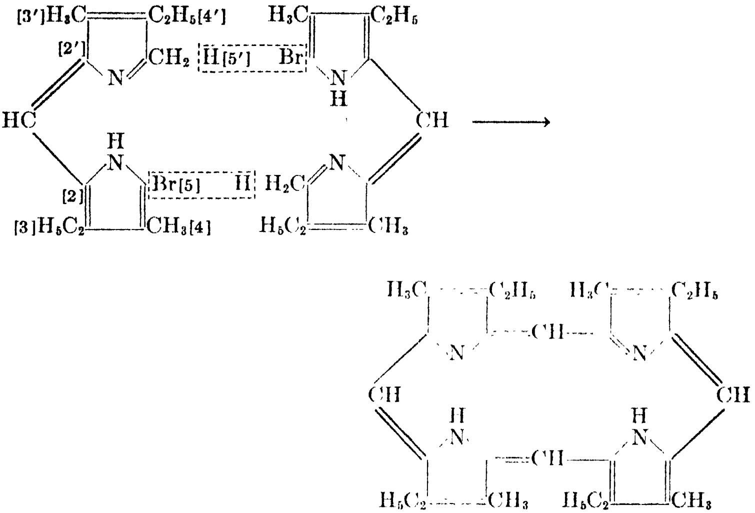
The same numbers can be used for the four isomers of coproporphyrin, with "tetrakis-(β-carboxyethyl)" in place of "tetraethyl-"; two of these isomers (I and III) have been isolated from the urine of patients suffering from porphyria.

An added proof for the correctness of the porphine formula is the existence of all the isomers predicted by it, which have been made accessible by the synthetic work of *H. Fischer*.

Synthesis of Porphine Derivatives

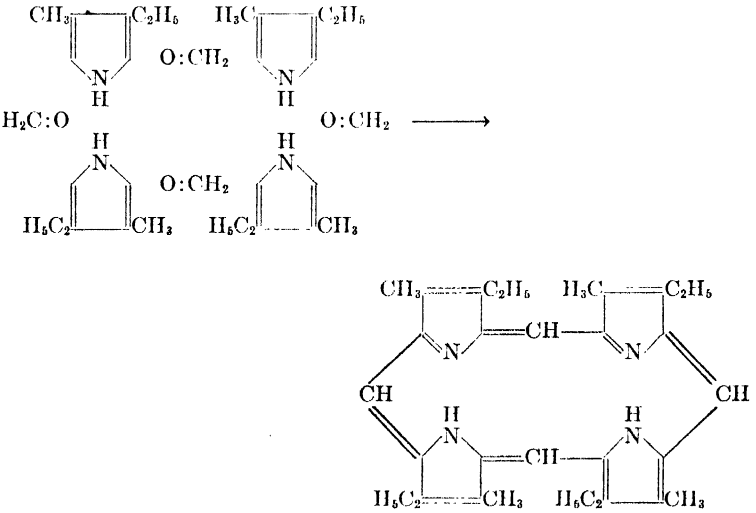
Syntheses of porphine derivatives usually start from bicyclic dipyrrylmethanes or -methenes. Of the numerous methods which have been used only those having the widest application will be given here.

1. Etioporphyrin I (see above) was first prepared by the action of concentrated sulfuric acid on 2 mols of brominated cryptopyrrylmethene, 2-(3-ethyl-4-methyl-5-bromo-2-pyrrylmethylene)-3,5-dimethyl-4-ethylpyrrolenine (*Fischer, Klarer*, Ann. **448**, 178):

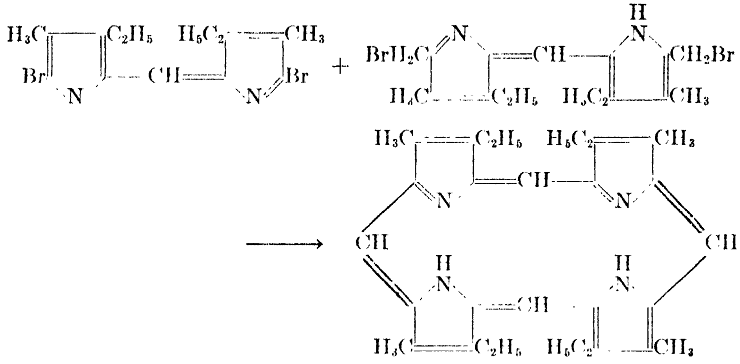


Other porphyrins can be obtained by using various methenes in this reaction.

2. The formation of etioporphyrin I by the condensation of opsopyrrole (4-ethyl-3-methylpyrrole), formaldehyde and formic acid is a clear-cut synthesis (*Fischer, Andersag,* Ann. **450**, 204; *Fischer, Halbig, Walach,* Ann. **452**, 268):



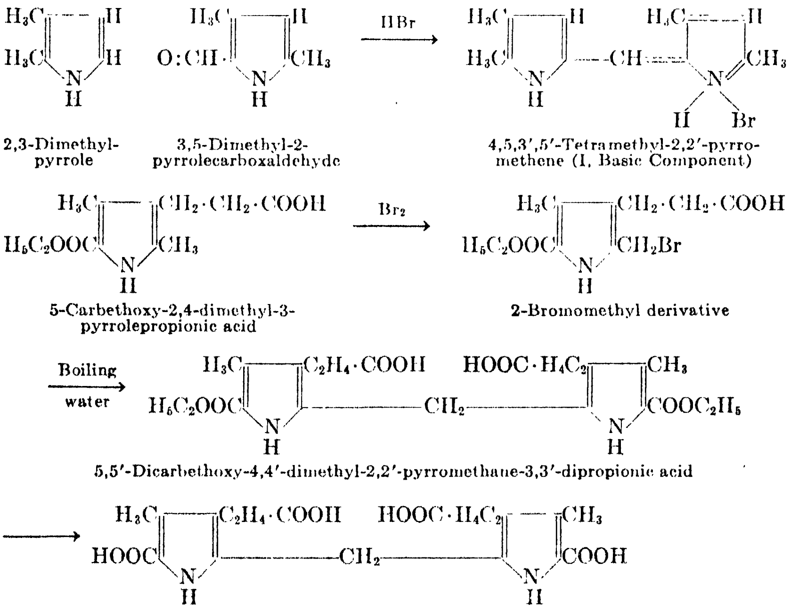
3. A porphyrin synthesis of wide applicability consists in fusing in succinic acid a dipyrrylmethene having two bromine atoms substituted on the nucleus with a dipyrrylmethene brominated in a methyl group. For etioporphyrin II the reaction is this:



Etioporphyrin II

Hemin is derived from a compound similar to etioporphyrin III, formulated on p. 42, but with the ethyl groups in the 2- and 4-positions replaced by vinyl groups. Elimination of the iron in hemin leaves the corresponding protoporphyrin: 2,4-divinyl-1,3,5,8-tetramethylporphine-6,7-dipropionic acid. The direct synthesis of porphyrins having unsaturated side-chains has not been accomplished up to the present time. However, it is possible to synthesize porphyrins containing free methine groups, for example, in positions 2 and 4 of the porphine nucleus; these are termed *deuteroporphyrins*. The deuteroporphyrin corresponding to etioporphyrin III, which has been synthesized (*Fischer, Kirstahler*, Ann. **466**, 183), can be converted to protoporphyrin by intermediate formation of 2,4-diacetyldeuteroporphyrin.

The complete synthesis of protoporphyrin and of hemin follows this course (*Fischer*, N. **1929**, 616; *Fischer, Zeile*, Ann. **468**, 114):



2,3-Dimethylpyrrole

3,5-Dimethyl-2-pyrrolecarboxaldehyde

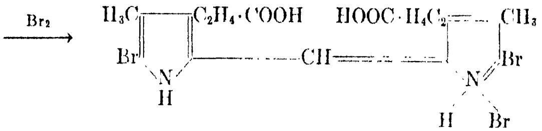
4,5,3',5'-Tetramethyl-2,2'-pyrromethene (I, Basic Component)

5-Carbethoxy-2,4-dimethyl-3-pyrrolepropionic acid

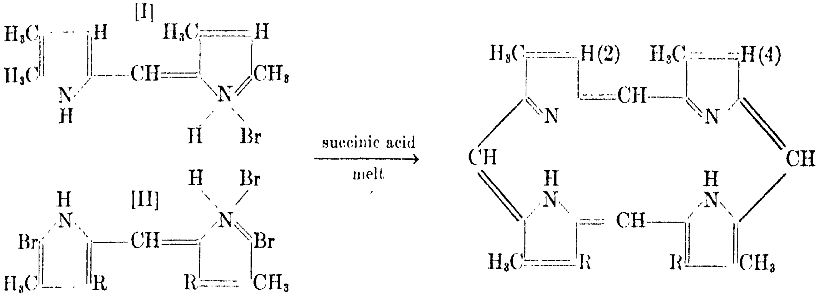
2-Bromomethyl derivative

5,5'-Dicarbethoxy-4,4'-dimethyl-2,2'-pyrromethane-3,3'-dipropionic acid

Free tetracarboxylic acid



5,5′-Dibromo-4,4′-dimethyl-2,2′-pyrromethene-3,3′-dipropionic acid (II, acid component)

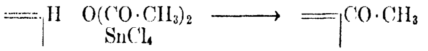


[R = —$CH_2 \cdot CH_2 \cdot COOH$]

Deuteroporphyrin

(Contains 2 free methine groups in the 2- and 4-positions)

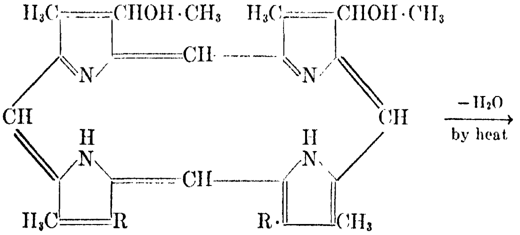
The two vinyl groups are introduced into positions 2 and 4 in this way:



$$=H \;\; \underset{SnCl_4}{O(CO \cdot CH_3)_2} \longrightarrow \; =CO \cdot CH_3$$

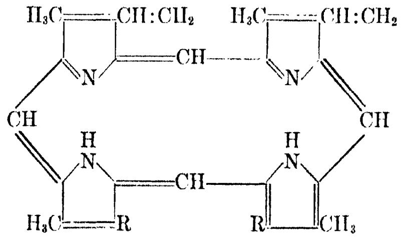
Diacetyldeuteroporphyrin

Reduction with potassium and alcohol gives:



Hematoporphyrin

(R = —$CH_2 \cdot CH_2 \cdot COOH$)



Protoporphyrin (introduction of iron ⟶ **hemin**)

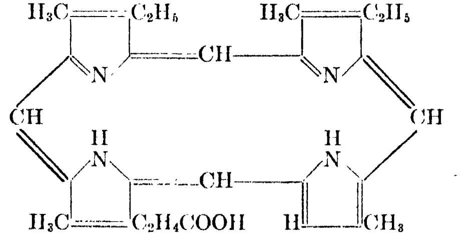
($CH{:}CH_2 \longrightarrow C_2H_5$, *mesoporphyrin*)

CHLOROPHYLL. The principal facts concerning this pigment of all green plants have been given in Vol. I, p. 552. Intensive investigation of the constitution of chlorophyll has clarified the constitution of several of the degradation products. For example, phytol (Vol. I, p. 152) has been synthesized (*Fischer, Löwenberg*, Ann. **475**, 183). The molecular formulas of phytochlorine e (chlorine e_6) and phytorhodine g have been corrected to $C_{35}H_{40}O_7N_4$ and $C_{35}H_{38}O_8N_4$, respectively, from the earlier ones $C_{34}H_{36}O_6N_4$ and $C_{34}H_{34}O_7N_4$ (*Treibs, Wiedemann*, Ann. **466**, 264).

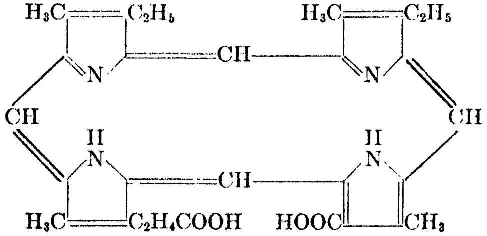
The most important advances in clarifying the constitution of chlorophyll concern the porphyrins formed by alkaline degradation of phytochlorine e and phytorhodine g. On heating with KOH in methyl alcohol, these first form dicarboxylic acids, *verdoporphyrin* and *rhodoporphyrin*, $C_{32}H_{34}O_4N_4$; then monocarboxylic acids, *phylloporphyrin* and *pyrroporphyrin*, $C_{31}H_{34}O_2N_4$. Phylloporphyrin is converted into pyrroporphyrin, which is the most stable porphyrin under the conditions of alkaline degradation.

Phyllo- and pyrroporphyrin, which are monocarboxylic acids, can be decarboxylated to phylloetioporphyrin, $C_{30}H_{34}N_4$, and pyrroetioporphyrin, $C_{30}H_{34}N_4$, respectively; the products are acid-free elementary porphyrins of the chlorophyll series. The earlier conclusion, that etioporphyrin from plant pigment has the same empirical formula as that from blood pigment, has not been verified subsequently. Etioporphyrin from blood pigment, $C_{32}H_{38}N_4$, and etioporphyrin from chlorophyll, $C_{30}H_{34}N_4$, differ by C_2H_4, which corresponds to the removal of a free methine group in a 2-position.

The arrangement of the side-chains in the porphyrins derived from chlorophyll has been determined by synthesis (synthesis of rhodo- and pyrroporphyrin: *Fischer, Berg, Schormüller*, Ann. **480**, 113; for the synthesis of the porphine nucleus, see p. 42):



Pyrroporphyrin: $C_{31}H_{34}O_2N_4$
2,4-Diethyl-1,3,5,8-tetramethylporphine-7-propionic acid



Rhodoporphyrin: $C_{32}H_{34}O_4N_4$
6-Carboxy-2,4-diethyl-1,3,5,8-tetramethylporphine-7-propionic acid.

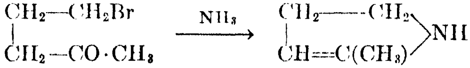
Pyrroetioporphyrin, $C_{30}H_{34}N_4$, is formed from pyrroporphyrin by decarboxylation, the propionic acid group being converted into an ethyl group.

These results show that the blood pigment porphyrins and the chlorophyll porphyrins have the same sequence of substituents in the β-positions, as well as the same porphine nucleus (see p. 42). Both classes of porphyrins are related to etioporphyrin III (see p. 42).

HYDROPYRROLES. Reduction of pyrrole and homologous pyrroles with zinc dust and acetic acid or mineral acids (*Knorr, Rabe*, Ber. **34,** 3491; *Ciamician*, Ber. **34,** 3952), or by electrolysis in slightly acid solution (Ger. Pat. 127086, 1901), gives dihydropyrroles (pyrrolines). Two more hydrogen atoms are added through the action of HI and phosphorus, yielding tetrahydropyrroles (pyrrolidines), which are also obtained directly by reduction of pyrroles with hydrogen over finely divided nickel at 190° (*Putochin*, Ber. **55,** 2742), and with hydrogen and platinum black in acetic acid solution (*Willstätter, Hatt*, Ber. **45,** 1477; *Hess*, Ber. **46,** 3120). The addition of hydrogen changes the nature of pyrrole considerably. While pyrrole is a very weak base, the pyrrolines and pyrrolidines behave like the strongly basic secondary amines of the aliphatic series.

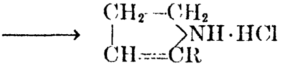
In the transition from pyrroles to pyrrolines, the addition of hydrogen probably takes place in the 1,4-positions, as in other compounds with *conjugated double bonds* (Vol. I, p. 28), with the formation of 2,5-*dihydropyrrole* (3-pyrroline).

2-PYRROLINES, 4,5-*dihydropyrroles*, are synthesized from the unstable γ-amino ketones or from γ-bromo ketones and ammonia or primary amines:



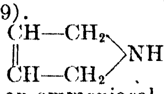
Another method of synthesizing this ring consists in reacting γ-chlorobutyronitrile with Grignard compounds:

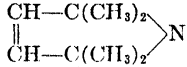
$$Cl{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CN + R{\cdot}MgCl \longrightarrow Cl{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}C{:}(NMgCl){\cdot}R \quad (I)$$

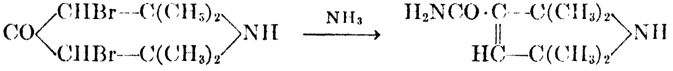


The ketimine derivative (I) first formed sometimes rearranges to a pyrroline hydrochloride (*Lipp, Seeles*, Ber. **62,** 2456).

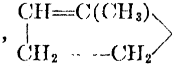
The 2-pyrrolines differ from the 3-pyrrolines, obtained by reduction of pyrroles, in that they resinify in air and are reduced by tin and hydrochloric acid to pyrrolidines. Treatment with benzoyl chloride and aqueous sodium hydroxide splits the 4,5-dihydropyrroles to γ-benzoylamino ketones; this conversion is particularly smooth with N-aryl-2-pyrrolines, which are usually stable only in the form of their salts (*Markwalder*, J.pr. **75,** 329).

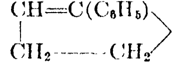
3-PYRROLINE, 2,5-*dihydropyrrole*,  b.p. 91° (748 mm.), is a water-soluble secondary base with an ammoniacal odor, which forms stable salts with acids (hydrochloride, m.p. 173°), absorbs CO_2 from the air, reacts with nitrous acid to form a nitrosamine, $C_4H_6N{\cdot}NO$, m.p. 38°, and with methyl iodide to form a dimethylpyrrolinium iodide, $C_4H_6N(CH_3)_2I$, etc. **1-Methylpyrroline**, $C_4H_6N{\cdot}CH_3$, b.p. 80°, is prepared by reduction of 1-methylpyrrole; it occurs in small amount among the tobacco alkaloids (*Pictet, Court*, Ber. **40,** 3775). **2,5-Dimethylpyrroline**, $(CH_3)_2C_4H_4{:}NH$, b.p. 106°, **2,3-dimethylpyrroline**, b.p. 121°, **1,2,5-trimethylpyrroline**, $(CH_3)_2C_4H_4{:}N(CH_3)$, b.p. 105–120°, from the corresponding pyrroles.

2,2,5,5-Tetramethylpyrroline, 
$\left.\begin{array}{l}\mathrm{CH{-}C(CH_3)_2}\\ \|\\ \mathrm{CH{-}C(CH_3)_2}\end{array}\right>\mathrm{NH}$, b.p. 114–116°, is formed in the distillation of **tetramethylpyrroline-3-carboxylic acid,** m.p. 300°. Its amide, m.p. 180° is prepared by the reaction of 3,5-dibromo-2,2,6,6-tetramethyl-4-piperidone with ammonia, analogous to the rearrangement of naphthalenes to indenes (*Pauly*, Ann. **322**, 77; *Pauly*, *Schaum*, Ber. **34**, 2287; *Pauly*, *Hültenschmidt*, Ber. **36**, 3371):

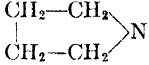


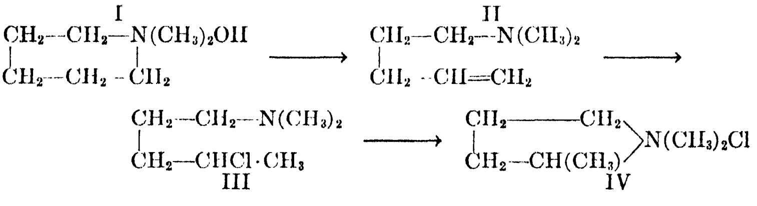
$$\mathrm{CO}\left<\begin{array}{l}\mathrm{CHBr{-}C(CH_3)_2}\\ \mathrm{CHBr{-}C(CH_3)_2}\end{array}\right>\mathrm{NH} \xrightarrow{\mathrm{NH_3}} \left.\begin{array}{l}\mathrm{H_2NCO{\cdot}C{-}C(CH_3)_2}\\ \quad\;\|\\ \quad\mathrm{HC{-}C(CH_3)_2}\end{array}\right>\mathrm{NH}$$

2-Methyl-2-pyrroline, 
$\left.\begin{array}{l}\mathrm{CH{=}C(CH_3)}\\ |\\ \mathrm{CH_2{-}{-}CH_2}\end{array}\right>\mathrm{NH}$, b.p. 45° (100 mm.), is synthesized from γ-aminopropyl methyl ketone or from γ-bromopropyl methyl ketone, $\mathrm{BrCH_2{\cdot}CH_2{\cdot}CH_2{\cdot}COCH_3}$, and alcoholic ammonia; it resinifies in air, and is reduced by Sn and HCl to methylpyrrolidine (*Gabriel*, Ber. **42**, 1241).

2-Phenyl-2-pyrroline, 
$\left.\begin{array}{l}\mathrm{CH{=}C(C_6H_5)}\\ |\\ \mathrm{CH_2{-}{-}{-}CH_2}\end{array}\right>\mathrm{NH}$, m.p. 45°, b.p. 249°, b.p. 118° (11 mm.), is formed by the removal of a water molecule from the unstable γ-aminobutyrophenone (*Gabriel*, *Colman*, Ber. **41**, 518), or according to the equation on p. 47 (*Lipp*, *Seeles*, Ber. **62**, 2456).

2-Chloropyrroline, $\mathrm{C_4H_6Cl{:}NH}$, m.p. 51°, is obtained from pyrrolidone or butyrolactam and $\mathrm{PCl_5}$; it resinifies readily (*Tafel*, *Wassmuth*, Ber. **40**, 2841).

PYRROLIDINE, tetramethylenimine, 
$\left.\begin{array}{l}\mathrm{CH_2{-}CH_2}\\ |\\ \mathrm{CH_2{-}CH_2}\end{array}\right>\mathrm{NH}$, b.p. 87°, gold salt: m.p. 206°, and its homologues have been partially covered in Vol. I, pp. 386, 598. For the ring-synthesis of pyrrolidine, 1,4-dibromobutane is reacted with *p*-toluenesulfonamide (*Müller*, *Sauerwald*, Mo. **48**, 153), or δ-chlorobutylamine is treated with acid-splitting agents (*Putochin*, Ber. **55**, 2747). Succinimide and its alkyl derivatives are converted to pyrrolidines in good yield by the *Tafel* method (Ber. **33**, 2209) of electrolytic reduction (*Späth*, *Breusch*, Mo. **50**, 349). An interesting method of preparation depends on transition of the six-membered piperidine ring to the five-membered pyrrolidine ring. Piperidine reacts with methyl iodide to form dimethylpiperidinium iodide, whose hydroxide (I) is opened by distillation to N,N-*dimethyl-4-pentenylamine* (II); the addition product of the latter with hydrogen chloride (III) rearranges readily to 1,1,2-trimethylpyrrolidinium chloride (IV):



$$\underset{\text{I}}{\begin{array}{l}\mathrm{CH_2{-}CH_2{-}N(CH_3)_2OH}\\ |\qquad\quad |\\ \mathrm{CH_2{-}CH_2{-}CH_2}\end{array}} \longrightarrow \underset{\text{II}}{\begin{array}{l}\mathrm{CH_2{-}CH_2{-}N(CH_3)_2}\\ |\\ \mathrm{CH_2{-}CH{=}CH_2}\end{array}} \longrightarrow$$

$$\underset{\text{III}}{\begin{array}{l}\mathrm{CH_2{-}CH_2{-}N(CH_3)_2}\\ |\\ \mathrm{CH_2{-}CHCl{\cdot}CH_3}\end{array}} \longrightarrow \underset{\text{IV}}{\left.\begin{array}{l}\mathrm{CH_2{-}{-}{-}CH_2}\\ |\\ \mathrm{CH_2{-}CH(CH_3)}\end{array}\right>\mathrm{N(CH_3)_2Cl}}$$

This transformation of permethylated piperidine to an unsaturated aliphatic amine (*Hofmann* degradation by exhaustive methylation) is a characteristic reaction for completely hydrogenated cyclic bases. Repetition of the operation leads to removal of the nitrogen as *trimethylamine*, leaving a nitrogen-free hydrocarbon residue. When N,N-dimethylpyrrolidinium iodide, prepared from pyrrolidine and methyl iodide, is distilled with KOH, N,N-dimethyl-3-butenylamine is formed; the methyl iodide addition product of the latter is decomposed by distillation with KOH into trimethylamine and an unsaturated hydrocarbon, 1,3-*butadiene*, the so-called *pyrrolylene*. In the same way 2-methyl-1,3-butadiene, or isoprene, is obtained from **3-methylpyrrolidine** (*Euler*, Habilitationsschrift, Leipzig, 1897; C. **1898**, **I**, 247). **1-Benzoylpyrrolidine,** b.p. 191° (12 mm.), is converted by PCl_5 or PBr_5 to 1,4-dichloro- or dibromobutane (*Knorr, Schneider*, Ber. **39**, 1419):

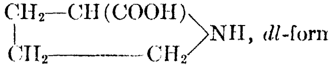
$$(CH_2)_4N \cdot COC_6H_5 \longrightarrow (CH_2)_4N \cdot CCl_2C_6H_5 \longrightarrow Cl(CH_2)_4Cl + NC \cdot C_6H_5$$

N-Alkylpyrrolidines, like other completely hydrogenated cyclic bases, are split by cyanogen bromide to cyanamide derivatives (*v. Braun*, Ber. **44**, 1252).

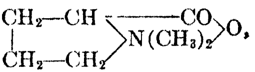
1-Methylpyrrolidine, $(CH_2)_4NCH_3$, b.p. 79°, is best prepared by catalytic hydrogenation of 1-methylpyrrole with platinum oxide + H_2 (*Wibaut*, Rec. **44**, 1101) or with Pd and H_2 at 160° (*Zelinsky, Jurjew*, Ber. **62**, 2589); it can also be obtained from N-methylbutylamine, $CH_3 \cdot CH_2 \cdot CH_2 \cdot CH_2NHCH_3$, by bromination with sodium hypobromite, followed by removal of HBr with concentrated sulfuric acid (*Löffler, Freytag*, Ber. **42**, 3427; *Löffler*, Ber. **43**, 2035). It is formed in the cleavage of the alkaloid nicotine, 1-methyl-2-(3-pyridyl)-pyrrolidine, with silver oxide (*Pictet*, Ber. **38**, 1951), and by heating hygrinic acid (see below).

2-Methylpyrrolidine, b.p. 95°, prepared from γ-aminovalerolactam by reduction with sodium and amyl alcohol, or from 2-methylpyrroline (page 48) with tin and hydrochloric acid, is converted to 2-methylpyrrole by heating with zinc dust. **3-Methylpyrrolidine**, picrate m.p. 106° (*Spath, Prokopp*, Ber. **57**, 474). **2-Ethylpyrrolidine**, b.p. 122° (744 mm.), picrate, m.p. 85°, is formed by the intramolecular rearrangement of hexamethylenediamine hydrochloride on heating (*Müller, Wachs*, Mo. **53/54**, 420).

2,4-Dimethylpyrrolidine, b.p. 115–117°. **1,2,2-Trimethylpyrrolidine**, b.p. 109–113° (*Knorr, Rabe*, Ber. **34**, 3498). **3-Phenylpyrrolidine**, b.p. 122° (12 mm.), picrate, m.p. 166°. **3,4-Diphenylpyrrolidine**, b.p. 200° (14 mm.) (*Spath, Breusch*, Mo. **50**, 349).

PROLINE, 2-pyrrolidinecarboxylic acid,  $\begin{matrix}CH_2-CH(COOH)\\ |\qquad\qquad\qquad\\ CH_2-\!\!-\!\!-\!\!-\!\!-CH_2\end{matrix}\Big>NH$, *dl*-form, m.p. 205° (anhydrous), picrate m.p. 135°, ethyl ester b.p. 80° (13 mm.), is present in its levorotatory form, m.p. 215° (anhydrous), $[\alpha]_D^{18} = -86.6°$ (aqueous solution), picrate m.p. 152°, among the hydrolytic cleavage products of numerous proteins, such as casein and gelatin (*Fischer, Abderhalden*, Ber. **37**, 3071), wheat gliadin [*Town*, Biochem.J. 22 (1928), 1083]. Isolation from the cleavage products with Reinecke-acid (*Kapfhammer, Eck*, Z.physiol.Chem. **170**, 294), by formation of the benzylidene derivative (*Bergmann, Zervas*, Z.physiol. Chem. **152**, 282), or of 1,5-trimethylenehydantoin, m.p. 165° [*Dakin*, Biochem.J. **12** (1918), 290]. Racemic proline is synthesized from bromo-γ-bromopropylmalonic ester, $BrCH_2CH_2CH_2 \cdot CBr(CO_2R)_2$, and ammonia, with subsequent saponification by hydrochloric acid or aqueous barium hydroxide solution (*Willstätter, Ettlinger*, Ann. **326**, 91), from δ-bromo-α-aminovaleric acid (the fission product of bromopropylphthalimidomalonic ester) and from δ-benzoylamino-α-bromovaleric acid (*Fischer, Zemplén*, Ber. **42**, 1022), or directly from aminomalonic ester (*Putochin*, Ber. **56**, 2213). The *m*-nitrobenzoyl derivative of racemic proline can be resolved into its optically active components by means of cinchonine (*Fischer, Zemplén*, Ber. **42**, 2992). Pyrrolidone-2-carboxylic acid (pyrroglutamic acid) is converted to proline by reduction of its ester with Na and alcohol (*Fischer, Boehner*, Ber. **44**, 1332). A dipeptide, *l*-N-prolyl-β-phenylalanine, $\overline{NH \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CH} \cdot CONHCH(CO_2H)CH_2C_6H_5$, is found among the hydrolytic cleavage products of *gliadin* (*Fischer, Luniak*, Ber. **42**, 4752). This and several other prolinepeptides have been obtained synthetically.

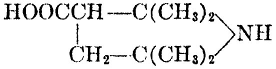
1-Methylpyrrolidine-2-carboxylic acid, *hygrinic acid*, m.p. 169°, is obtained by the oxidation of hygrin, the alkaloid found in cocoa leaves. Its synthesis is analogous to that of proline, from bromo-γ-bromopropylmalonic ester and methylamine (*Willstätter, Ettlinger*, Ann. **326**, 91). On heating it decomposes into CO_2 and 1-methylpyrrolidine (see above).

The methylbetaine of hygrinic acid is **stachydrine**,  $\begin{matrix}CH_2-CH\,-\!\!-\!\!-\!\!-CO\\ |\qquad\qquad\qquad\\ CH_2-CH_2\qquad\qquad\end{matrix}\Big>N(CH_3)_2\Big>O$, m.p. 210° (anhydrous), which has been isolated from the bulbs of *Stachys tuberifera*, from the leaves of *Citrus aurantium* (*Schulze, Trier*, Ber. **42**, 4654) and from alfalfa [*Steenbock*, J.Biol.Chem. **35**, (1919), 1].

1-Methylpyrrolidine-2,5-dicarboxylic acid, m.p. 274° (dec.), from α,α-dibromoadipic ester with methylamine (*Willstätter, Lessing*, Ber. **35**, 2065).

5-Carboxymethyl-1-methylpyrrolidine-2-carboxylic acid is identical with the tropinic acid resulting from oxidation of *tropine* and *ecgonine* (*Willstätter*, Ber. **31**, 1534; *Willstätter, v. Sicherer*, Ber. **32**, 1290). The conversion of this acid to pimelic acid by removal of the nitrogen by exhaustive methylation and subsequent reduction provides the key to the constitution of the tropane alkaloids (*Willstätter, Bode*, Ber. **33**, 414).

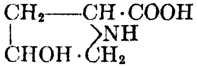
2,2,5,5-Tetramethylpyrrolidine-3-carboxylic acid,



$$\begin{array}{l} HOOCCH—C(CH_3)_2\diagdown \\ |\qquad\qquad\qquad\quad > NH \\ CH_2—C(CH_3)_2\diagup \end{array}$$

m.p. 220° (dec.); the amide of this acid is prepared from tetramethylpyrrolinecarboxylic acid amide by reduction with sodium amalgam. With KOBr the amide yields 3-aminotetramethylpyrrolidine, b.p. 174°, a strong diacid base.

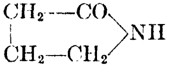
Hydroxyproline, *4-hydroxypyrrolidine-2-carboxylic acid,*



$$\begin{array}{l} CH_2——CH\cdot COOH \\ |\qquad\qquad > NH \\ CHOH\cdot CH_2 \end{array}$$

m.p. 270°, $[\alpha]_D = -80.6°$ (in water), picrate m.p. 188°, was obtained in the levorotatory form by the hydrolysis of various proteins, first from gelatin (*Fischer*, Ber. **35**, 2660) and later from casein and edestin. Isolation from the products of hydrolysis: *Kapfhammer, Eck*, Z.physiol.Chem. **170**, 294. Synthesis: *Leuchs, Brewster*, Ber. **46**, 986; *Leuchs, Bormann*, Ber. 52, 2086; *Traube, Johow, Tepohl*, Ber. **56**, 1861. Since hydroxyproline contains two asymmetric carbon atoms, four isomers are obtained. The so-called α-compound yields on fission a levorotatory proline, which is identical with natural proline.

The lactams of γ-amino acids, such as **butyrolactam,** 2-**pyrrolidone,**

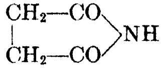


$$\begin{array}{l} CH_2—CO\diagdown \\ |\qquad\qquad > NH \\ CH_2—CH_2\diagup \end{array}$$

have been described in Vol. I (p. 450). The best general method for their preparation is the electrolytic reduction of succinimide and its derivatives (*Huth*, Ber. **33**, 2209).

A derivative of 2-oxopyrrolidine or 2-pyrrolidone is **5-carboxymethyl-1-methyl-2-pyrrolidone, ecgoninic acid,** *dl*-form, m.p. 94°, *levo*-form, m.p. 117°, which is an oxidation product of tropane alkaloids, and also of tropinic acid.

The imides of the succinic acid series, such as **succinimide,**

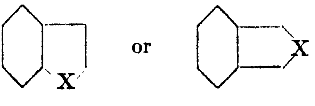


$$\begin{array}{l} CH_2—CO\diagdown \\ |\qquad\qquad > NH, \\ CH_2—CO\diagup \end{array}$$

(Vol. I, p. 552), are **2,5-dioxopyrrolidines.**

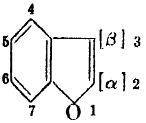
Condensed Nuclei Containing Furan, Thiophene, and Pyrrole Rings

Condensed nuclei of this type consist of a furan, thiophene, or pyrrole ring sharing two adjacent carbon atoms with an aromatic ring such as benzene or naphthalene. Either the 2,3- or the 3,4-carbons atoms of the heterocyclic ring can be shared:

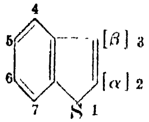


Only members of the first class are important, although members of the second class have been synthesized also.

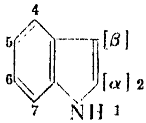
The following series of condensed nuclei are derived from furan, thiophene, and pyrrole:



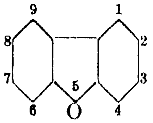
Benzofuran
Coumarone



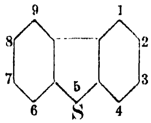
Benzothiophene
Thianaphthene



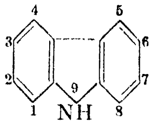
Benzopyrrole
Indole



Dibenzofuran
Diphenylene oxide



Dibenzothiophene
Diphenylene sulfide



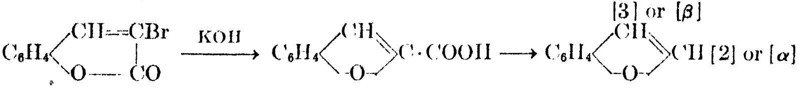
Dibenzopyrrole
Carbazole

The numberings are those given in "The Ring Index," in which carbazole is one of the few compounds whose standard numbering is the one fixed by usage, and not the one corresponding to the "Proposed International Rules for Numbering Organic Ring Systems."

Condensed nuclei in which two heterocyclic rings participate in the formation of one benzene ring are also known.

5. BENZOFURANS

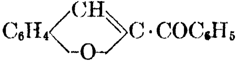
The benzofurans are also termed "coumarones" because of their formation from derivatives of coumarin (1,2-benzopyrone). They are prepared: (*1*) By the action of alcoholic KOH on coumarin dibromide or 3-bromocoumarin (*Fittig*, Ann. **216**, 162):



$$C_6H_4{<}\begin{smallmatrix}CH{=}CBr\\ |\quad\ \ |\\ O\text{—}CO\end{smallmatrix} \xrightarrow{KOH} C_6H_4{<}\begin{smallmatrix}CH\\ O\end{smallmatrix}{>}C\cdot COOH \longrightarrow C_6H_4{<}\begin{smallmatrix}CH\\ O\end{smallmatrix}{>}CH$$

3-Bromocoumarin Coumarilic acid Benzofuran
Coumarone

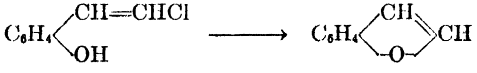
Other coumarins, such as umbelliferone, esculetin, and daphnetin, react similarly; α-bromo-*o*-hydroxycinnamic acid and its homologues are formed as intermediate products; they split off HBr to give the benzofurans. 2-Benzoylbenzofuran,



$$C_6H_4{<}\begin{smallmatrix}CH\\ O\end{smallmatrix}{>}C\cdot COC_6H_5$$

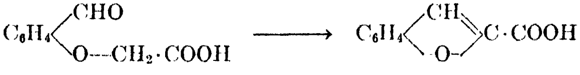
is produced by analogous reactions between α,β-dibromo-β-*o*-acetoxyphenylpropiophenone (acetyl-*o*-hydroxybenzylideneacetophenone dibromide) and KOH (*v. Kostanecki, Tambor*, Ber. 29, 237), and between salicylaldehyde, α-bromoacetophenone and KOH (*Rap*, Gazz. 25, II, 285). For the preparation of related compounds see *Tambor*, *Gubler*, Helv. **2**, 101.

(*2*) β-Chloro-*o*-hydroxystyrene is condensed by KOH to benzofuran:



$$C_6H_4{<}\begin{smallmatrix}CH{=}CHCl\\ OH\end{smallmatrix} \longrightarrow C_6H_4{<}\begin{smallmatrix}CH\\ O\end{smallmatrix}{>}CH$$

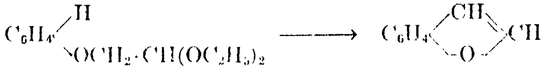
(*3*) *o*-Formylphenoxyacetic acid, when warmed with acetic anhydride and sodium acetate, forms coumarilic acid (*Rössing*, Ber. **17**, 3000):



$$C_6H_4{<}\begin{smallmatrix}CHO\\ O\text{—}CH_2\cdot COOH\end{smallmatrix} \longrightarrow C_6H_4{<}\begin{smallmatrix}CH\\ O\end{smallmatrix}{>}C\cdot COOH$$

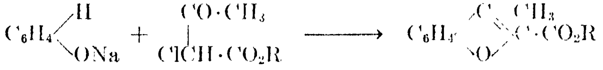
The acetic acid derivatives of *o*-hydroxy ketones react in the same way (*v. Kostanecki, Tambor*, Ber. 42, 901).

(*4*) Benzofuran is prepared from phenoxyacetal with zinc chloride in glacial acetic acid:



A large number of alkylbenzofurans have been obtained by the condensation of homologues of phenoxyacetal and of phenoxyacetone, $C_6H_5 \cdot O \cdot CH_2COCH_3$, by means of sulfuric acid (*Stoermer*, Ann. **312**, 237).

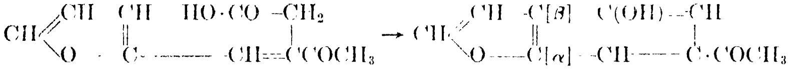
(*5*) A reaction similar to the formation of coumarins from phenol and malic acid or acetoacetic ester (Vol. III, p. 174) produces benzofurans from sodium phenolate and α-chloroacetoacetic ester (*Hantzsch*, Ber. **19**, 1291):



3-Methylcoumarilic acid ester

Resorcinol and 2 mols of the ester form a *benzodifuran* derivative, pyrogallol and 3 mols of the ester, a *benzotrifuran* derivative, and naphthol, a *naphthofuran* derivative (p. 56). Similar to this reaction is the production of benzofurans and benzodifurans from quinones and chlorinated quinones, such as tetrachloroquinone, on heating with acetoacetic ester (*Ikuta*, J.pr. **45**, 67; *Graebe*, *Levy*, Ann. **283**, 245).

(*6*) In the methods given above, it is the furan ring which is formed; in the synthesis of 6-acetyl-4-hydroxybenzofuran, from β-2-furfurylidenelevulinic acid (*Kehrer*, *Kleberg*, Ber. **26**, 345), the benzene ring is closed:



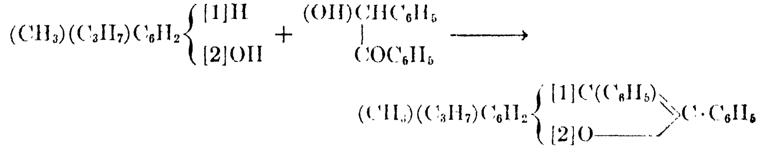
BENZOFURAN, COUMARONE, b.p. 177°, picrate m.p. 103°, is obtained by the distillation of coumarilic acid with lime, from β-chloro-o-hydroxystyrene, from phenoxyacetal with zinc chloride (*Stoermer*, Ber. **30**, 1703) and from coal tar [*Weissgerber*, *Moehrle*, Brennstoff-Chem. **4** (1923), 81], in which several methylbenzofurans are also found [*Auwers*, *Hampe*, Ber. **33**, 3014; *Boes*, Apoth. Z. 22 (1907), 177].

Benzofuran is readily polymerized by acids, particularly concentrated sulfuric acid and $SnCl_4$, to *paracoumarone*, m.p. 108°; the latter, on distillation, is partly depolymerized and partly decomposed to phenols. Solvent naphtha, which consists of benzofuran together with some indene derivatives, is polymerized on a commercial scale to *coumarone resins*, which are of use in the preparation of paints and varnishes. [Preparation, properties, analysis and uses of coumarone resins: *Marcusson*, Mitt.Materialprüfungsamt,Berlin-Lichterfelde West **38** (1921), 69; C. **1921, IV**, 1230.] On heating with alcoholic KOH at 200° benzofuran is decomposed into o-ethylphenol, o-hydroxystyrene, o-hydroxyphenylacetic acid, o-hydroxyphenylethanol and its anhydride which is a hydrogenated benzofuran (*Stoermer*, *Kahlert*, Ber. **34**, 1806; **35**, 1630).

For spectroscopic data on benzofurans, see *v. Auwers*, Ann. **408**, 260; **422**, 133. For the reaction with halogens, see page 53.

A series of benzofurans alkylated in either the benzene or the furan ring, or both, are synthesized by the methods described above: **2-methylbenzofuran,** b.p. 197°, from α-phenoxypropionacetal, **3-methylbenzofuran,** b.p. 193°, from phenoxyacetone or methylcoumarilic acid. Of the 15 possible dimethylbenzofurans, 11 are known: **2,3-Dimethylbenzofuran,** b.p. 210°, from dimethylcoumarilic acid. **2,5-Dimethylbenzofuran,** b.p. 220°. **2,7-Dimethylbenzofuran,** b.p. 215° (749 mm.). **2,3,5-Trimethylbenzofuran,** b.p. 100° (10 mm.), and other alkylbenzofurans, see *v. Auwers*, Ann. **422**, 133.

2-Phenylbenzofuran, m.p. 121°, from the sodium salt of salicylaldehyde and phenylchloroacetic acid (*cf.* Method *1*, p. 51, and *Stoermer*, Ber. **36**, 3979). **3-Phenylbenzofuran,** two modifications, m.p. 13° and 42°, b.p. 163° (9 mm.), from o-hydroxydiphenylethylene (Vol. III, p. 553) by treatment of its dibromide with Na alcoholate (*Stoermer*, *Kippe*, Ber. **36**, 4004). Both phenylbenzofurans can also be prepared from o-hydroxydiphenylacetic acid lactone (Vol. III, p. 556) by heating with PBr_3 (*Stoermer*, *Kippe*, Ber. **36**, 4006). 2,3-Diphenyl-benzofurans, such as **2,3-diphenyl-4-methyl-7-isopropylbenzofuran**, m.p. 116°, are obtained by condensation of phenols and benzoin in the presence of sulfuric acid [*Japp, Meldrum*, Proc.Roy.Soc. **15** (1899), 167]:



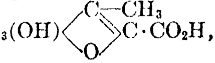
$$(CH_3)(C_3H_7)C_6H_2\begin{cases}[1]H\\ {[2]}OH\end{cases} + \begin{matrix}(OH)CHC_6H_5\\ |\\ COC_6H_5\end{matrix} \longrightarrow (CH_3)(C_3H_7)C_6H_2\begin{cases}[1]C(C_6H_5)\\ {[2]}O\text{———}\end{cases}\!\!>C\cdot C_6H_5$$

Benzofuran adds one molecule of chlorine or bromine. The dibromide, **2,3-dibromo-2,3-dihydrobenzofuran**, $C_8H_6Br_2O$, m.p. 86°, is readily converted to monobromobenzofuran; monochlorobenzofuran is obtained from the dichloride. Both these products can be further halogenated to dihalogenated benzofurans: **2,3-dichlorobenzofuran**, m.p. 26°, b.p. 226°, **dibromobenzofuran**, m.p. 27°, b.p. 270°. The monochlorobenzofuran is probably a mixture of 2- and 3-chlorobenzofuran, since on heating with alcoholic alkali to 180-190° it yields, among other products, 3(2)-benzofuranone, $C_6H_4\left<\begin{matrix}CO\\ O\end{matrix}\right>CH_2$, and *o*-hydroxyphenylacetic acid, whose lactone, $C_6H_4\left<\begin{matrix}CH_2\\ O\end{matrix}\right>CO$, reacts with PCl_5 to give pure **2-chlorobenzofuran**. When treated with sodium acetate benzofuran dichloride decomposes to *o*-hydroxyphenylglycolaldehyde, $C_6H_4\begin{cases}[1]OH\\ {[2]}CH(OH)CHO\end{cases}$, m.p. 64° (*Stoermer*, Ann. **313**, 79). When heated alone, benzofuran dibromide yields only **2-bromobenzofuran**, liquid, b.p. 221-223°, which can be synthesized from *o*-hydroxyphenylacetic acid lactone with $POBr_3$. When it is heated with alcoholic KOH, 2-bromobenzofuran is decomposed to *o*-hydroxyphenylacetic acid; under the same conditions benzofuran dibromide gives chiefly **3-bromobenzofuran**, m.p. 39°, b.p. 219 220°; when heated with alcoholic KOH, the latter compound forms 3-ethoxybenzofuran, together with some 2-ethoxybenzofuran and *o*-hydroxyphenylacetic acid (*Stoermer, Kahlert*, Ber. **35**, 1633).

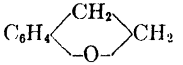
NITROBENZOFURANS. When 2-bromobenzofuran is treated with N_2O_3, bromine is liberated and **2-nitrobenzofuran**, m.p. 134°, is formed; it is also obtainable in small quantity by the nitration of benzofuran. 3-Bromobenzofuran and N_2O_3 give **3-bromo-2-nitrobenzofuran**, m.p. 132°. 2-Nitrobenzofuran is rearranged by sodium ethylate solution to the monoxime of 2,3-benzofurandione (Vol. III, p. 427): $C_6H_4\left<\begin{matrix}CH\\ O\end{matrix}\right>CNO_2 \longrightarrow C_6H_4\left<\begin{matrix}CO\\ O\end{matrix}\right>C{:}NOH$. *Cf.* the analogous rearrangements of 7-nitrostilbene, of 1- and 2-nitronaphthalenes (Vol. III, p. 614), of 9-nitrophenanthrene and of 9-nitroanthracene (Vol. III, p. 649) (*Stoermer, Kahlert*, Ber. **35**, 1633).

No aldehydes of the benzofuran series have been reported.

KETONES. **2-Acetylbenzofuran**, *2-benzofuryl methyl ketone*, $C_8H_5O(COCH_3)$, m.p. 75°, is prepared from salicylaldehyde with chloroacetone; with bromine it forms a bromide, $C_8H_5O(COCH_2Br)$, which condenses with a second molecule of salicylaldehyde to give **dibenzofuryl ketone**, $(C_8H_5O)_2CO$, golden yellow platelets, m.p. 154° (*Stoermer*, Ann. **312**, 333). Acetylbenzofuran is reduced by sodium and alcohol to α-methyl-2-benzofuranmethanol and 4-*o*-hydroxyphenyl-2-butanol, $HO[2]C_6H_4CH_2CH_2CH(OH)CH_3$ (*Stoermer, Schäffer*, Ber. **36**, 2863). **2-Benzoylbenzofuran**, $C_8H_5O(COC_6H_5)$, m.p. 91°, obtained from the acetyl derivative of *o*-hydroxyphenylacrylophenone dibromide and from salicylaldehyde with α-bromoacetophenone, is split by alkali fusion into benzofuran and benzoic acid (*v. Kostanecki, Tambor*, Ber. 29, 237; *Rap*, Gazz. **25**, II, 285).

CARBOXYLIC ACIDS. **Cumarilic acid**, *2-benzofurancarboxylic acid*, m.p. 190° from 3-bromocoumarin. For the esters, amide, chloride, hydrazide and azide, see *Stoermer, Calov*, Ber. **34**, 773. The azide forms with alcohol 2-benzofurancarbamic acid ester, $(C_8H_5O)NHCO_2C_2H_5$, m.p. 141°, which can be saponified to *o*-hydroxyphenylacetic acid. **3-Methylbenzofuran-2-carboxylic acid,** m.p. 189°, ester, m.p. 51°, is prepared according to Method *5*. **Hydroxytrichloro-3-methylbenzofuran-2-carboxylic acid,**  $C_6Cl_3(OH)\langle\underset{O}{\overset{C—CH_3}{}}\rangle C\cdot CO_2H$, m.p. 258°, from tetrachloroquinone and acetoacetic ester.

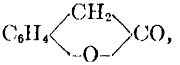
HYDROBENZOFURANS. 2,3-Dihydrobenzofuran, *coumaran,*

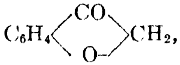
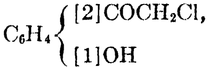
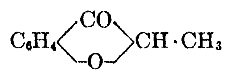


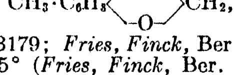
$$C_6H_4\langle\underset{-O-}{\overset{CH_2}{}}\rangle CH_2$$

b.p. 189°, is formed, together with *o*-ethylphenol, by reduction of benzofuran with sodium and alcohol (*Alexander*, Ber. **25**, 2409); it is synthesized from *o*-(2-bromoethyl)-phenol with sodium hydroxide solution, and from *β*,2-dibromophenetole, $BrC_6H_4OCH_2CH_2Br$, with sodium in ether. The latter method is also used to prepare **Bz-methyldihydrobenzofurans** (*Stoermer, Gohl*, Ber. **36**, 2873). **2-Phenyl-2,3-dihydrobenzofuran,** m.p. 32°, from 2-phenylbenzofuran with Na and alcohol, besides *o*-hydroxybibenzyl. **3-Phenyl-2,3-dihydrobenzofuran,** m.p. 38°, b.p. 167° (14 mm.), from **2-chloro-3-phenylbenzofuran,** which is prepared by treatment of *o*-hydroxydiphenylacetic acid lactone with PCl_5 (*Stoermer, Kippe*, Ber. **36**, 3992).

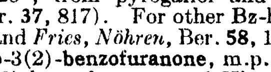
3-Amino-2,3-dihydrobenzofuran, b.p. 122° (18 mm.), by reduction of 3-benzofuranone oxime (*Stoermer, König*, Ber. **39**, 496). **2,3-Dihydrobenzofuran-2-carboxylic acid,** *hydrocoumarilic acid*, m.p. 116.5°, by reduction of coumarilic acid with sodium amalgam.

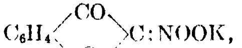
2(3)-**Benzofuranone,** 2-**coumaranone,**  $C_6H_4\langle\underset{-O-}{\overset{CH_2}{}}\rangle CO$, is considered as the lactone of *o*-hydroxyphenylacetic acid.

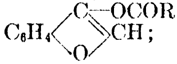
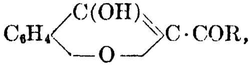
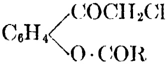
3(2)-**Benzofuranone,** 3-**coumaranone,**  $C_6H_4\langle\underset{O-}{\overset{CO}{}}\rangle CH_2$, m.p. 97°, is prepared: (*1*) By heating *o*-hydroxy-*α*-chloroacetophenone,  $C_6H_4\begin{cases}[2]COCH_2Cl,\\ [1]OH\end{cases}$ with sodium acetate (*Fries, et al.*, Ber. **41**, 4273; **43**, 214). (*2*) By condensation of phenoxyacetic acid, $C_6H_5O\cdot CH_2CO_2H$, with P_2O_5 (*Stoermer, Bartsch*, Ber. **33**, 3176). (*3*) From its carboxylic acid, whose ester, **2,3-dihydro-3-oxobenzofuran-2-carboxylic acid ester,**  $C_6H_4\langle\underset{-O-}{\overset{CO}{}}\rangle CHCO_2C_2H_5$, m.p. 66°, is obtained by condensation of the ester of *o*-carboxyphenoxyacetic acid with sodium (*Friedländer*, Ber. **32**, 1867; Ger. Pat. 105200, 1898; *Stoermer*, Ann. **312**, 258). This compound is the oxygen analogue of indoxyl; it is soluble in alkali, with enolization, but in other respects behaves as a ketone (forms oximes, semicarbazones, etc.). The methylene group is very active, condensing with aldehydes, nitrosodimethylaniline, and itself (see below). **2-Methyl-3(2)-benzofuranone,**

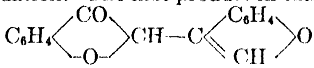
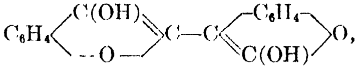
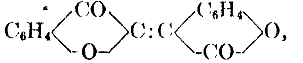


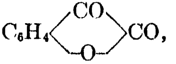
$$C_6H_4\langle\underset{-O-}{\overset{CO}{}}\rangle CH\cdot CH_3$$

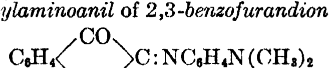
b.p. 163-165° (40 mm.), (*Stoermer, Atenstädt*, Ber. **35**, 3565). **5-, 6- and 7-Methyl-3(2)-benzofuranone,**  $CH_3\cdot C_6H_3\langle\underset{-O-}{\overset{CO}{}}\rangle CH_2$, m.p. 54°, 85°, and 102° (*Stoermer, Bartsch*, Ber. **33**, 3179; *Fries, Finck*, Ber. **41**, 4278). **5,7-Dimethyl-3(2)-benzofuranone,** m.p. 75° (*Fries, Finck*, Ber. **41**, 4278). **Bz-Dihydroxy-3(2)-benzofuranone,** m.p. 226°, from pyrogallol and chloroacetic acid with $POCl_3$ (*Feuerstein, Brass*, Ber. **37**, 817). For other Bz-hydroxy derivatives, see *Sonn, Patschke*, Ber. **58**, 96, and *Fries, Nöhren*, Ber. **58**, 1027.

2-Bromo- and **2,2-dibromo-3(2)-benzofuranone,** m.p. 86° and 142°, are prepared by bromination of 3(2)-benzofuranone. **2-Nitro-3(2)-benzofuranone** is obtained in the form of its potassium salt,  $C_6H_4<\begin{smallmatrix}CO\\ O\end{smallmatrix}>C:NOOK$, from 2-nitro-3-bromobenzofuran (p. 53) by reaction with dialkylamines, followed by treatment of the reaction product with alcoholic KOH (*Stoermer*, Ber. **42**, 200).

3(2)-Benzofuranone condenses with benzaldehyde to a benzylidene compound, m.p. 108°, and with *p*-nitrosodimethylaniline to the dimethylaminoanil of benzofurandione (see below). A series of substituted benzylidene-3(2)-benzofuranones are prepared from substituted benzylidene-*o*-hydroxyacetophenone dibromides (*Emilewicz, v. Kostanecki*, Ber. **31**, 699; **32**, 309; *Feuerstein, v. Kostanecki*, Ber. **31**, 1759; *v. Kostanecki, Rozycki*, Ber. **32**, 2257). The dibromides of benzylidene-3(2)-benzofuranones rearrange in dilute alkali to *flavonols* (*Auwers, Müller*, Ber. **41**, 4233). Acylation of 3(2)-benzofuranones in alkaline solution yields O-acyl-3-benzofuranols,  $C_6H_4<\begin{smallmatrix}C\text{—}OCOR\\ O\end{smallmatrix}>CH$; the isomeric C-acyl derivatives,  $C_6H_4<\begin{smallmatrix}C(OH)\\ O\end{smallmatrix}>C\cdot COR$, are obtained by ring-closure of acyl-*o*-hydroxy-α-chloroacetophenone,  $C_6H_4<\begin{smallmatrix}COCH_2Cl\\ O\cdot COR\end{smallmatrix}$, by means of potassium carbonate, during which the acyl group shifts to a carbon atom (*v. Auwers*, Ber. **43**, 2192).

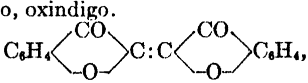
3(2)-Benzofuranone dissolves in alkali with formation of salts of 3-benzofuranol; in the air this solution rapidly turns blood-red, due to simultaneous condensation and oxidation. The first product in this transformation is an **oxodihydrobibenzofuran**,  $C_6H_4<\begin{smallmatrix}CO\\ O\end{smallmatrix}>CH\text{—}C<\begin{smallmatrix}C_6H_4\\ CH\end{smallmatrix}>O$, which adds oxygen to form **3,2′-dihydroxy-2,3′-bibenzofuran**,  $C_6H_4<\begin{smallmatrix}C(OH)\\ O\end{smallmatrix}>C\text{—}C<\begin{smallmatrix}C_6H_4\\ C(OH)\end{smallmatrix}>O$, orange-yellow needles, m.p. 185°. The latter is further oxidized by hydrogen peroxide to the oxygen analogue of indirubin (p. 81), **oxindirubin, $\Delta^{2,3'}$-bibenzofuran-3,2′-dione,**  $C_6H_4<\begin{smallmatrix}CO\\ O\end{smallmatrix}>C:C<\begin{smallmatrix}C_6H_4\\ CO\end{smallmatrix}>O$, orange-yellow needles which sublime without decomposition, m.p. 215°, which is also obtained by condensation of 3(2)-benzofuranone with benzofurandione or *o*-hydroxyphenylglyoxylic acid in concentrated sulfuric acid (*Fries, Pfaffendorf*, Ber. **43**, 212; **44**, 114).

2,3-Benzofurandione, *coumarandione,*  $C_6H_4<\begin{smallmatrix}CO\\ O\end{smallmatrix}>CO$, yellow plates, m.p. 134°, is the lactone of *o*-hydroxyphenylglyoxylic acid, from which it is obtained by heating in benzine solution with P_2O_5 or by distillation *in vacuo* (*Fries, Pfaffendorf*, Ber. **45**, 154). Bz-Alkylbenzofurandiones have been formed from substituted *o*-hydroxyphenylglyoxylic acids by heating with P_2O_5 in benzine solution. **4-Methyl-** and **5-methyl-2,3-benzofurandione**, m.p. 112° and 149° (*Fries*, Ber. **42**, 234). For other alkyl derivatives, see *v. Auwers*, Ber. **49**, 816; *Fries*, Ann. **442**, 254. The *4-dimethylaminoanil* of *2,3-benzofurandione*,



$$C_6H_4<\begin{smallmatrix}CO\\ O\end{smallmatrix}>C:NC_6H_4N(CH_3)_2$$

from 3(2)-benzofuranone and *p*-nitrosodimethylaniline (see above), combines with one molecule of 3(2)-benzofuranone to form a compound, $C_{24}H_{20}O_4N_2$, m.p. 203° (dec.), which is split by hydrochloric acid to N,N-dimethyl-*p*-phenylenediamine and the oxygen analogue of indigo, oxindigo.

Oxindigo, $\Delta^{2,2'}$*-bi-3(2)-benzofuranone,*  $C_6H_4<\begin{smallmatrix}CO\\ O\end{smallmatrix}>C:C<\begin{smallmatrix}CO\\ O\end{smallmatrix}>C_6H_4$, lemon-yellow prisms, m.p. 276°, sublimes undecomposed, forming a yellow vapor. It is also obtained from the potassium salt of 2-nitro-3(2)-benzofuranone (see above) by boiling with water or by treatment with bromine or iodine (*Fries, Hasselbach,* Ber. **44**, 124; *Stoermer, Brachmann*, Ber. **44**, 315; *Fries, et al.*, Ann. **405**, 316). As a derivative of furan, oxindigo is unstable to alkali, so vatting in alkaline solution is not possible; however, the diacetyl derivative of the leuco form can be obtained by reduction with zinc dust in the presence of acetic anhydride.

Oxidation with chromsulfuric acid gives 2,3-benzofurandione (p. 55).

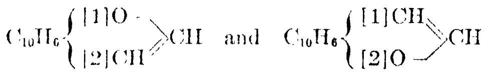
A number of substituted oxindigos have been obtained by the methods given above for oxindigo: 6,6′-*dimethyloxindigo* (*Fries, et al.*, Ann. **405**, 347); **4,4′,6,6′-tetramethyloxindigo**, yellow, m.p. 286° (*Fries*, Ann. **442**, 263); **6,6′-dimethoxyoxindigo**, m.p. 310°, yellow.

2-(3-Oxo-2-thianaphthenylidene)-3(2)-benzofuranone, benzofuran-thianaphthene-indigo, brick-red (*Fries, Bartholomäus*, Ann. **405**, 373).

By application of Method 5 (p. **52**) to polyhydroxybenzenes, benzodifurans and benzotrifurans are obtained.

Dimethylbenzodifurandicarboxylic acid ester, $C_6H_2\left\{\begin{matrix} C\cdot CH_3 \\ \quad\searrow C\cdot CO_2R \\ O \end{matrix}\right\}_2$, from resorcinol and chloroacetoacetic acid ester, α-compound, m.p. 186°, β-compound, m.p. 141°. **3,5,9-Trimethylbenzo[1,2-*b*, 3,4-*b*′, 5,6-*b*″]trifuran-2,5,8-tricarboxylic acid ester**, $C_6\left\{\begin{matrix} C\cdot CH_3 \\ \quad\searrow C\cdot CO_2R \\ O \end{matrix}\right\}_3$, m.p. 297° (dec.), from phloroglucinol and chloroacetoacetic acid ester.

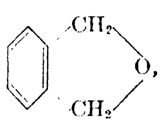
The corresponding **naphthofurans** are also known: **Naphtho[1,2-*b*]furan** and **naphtho[2,1-*b*]furan**, α- and β-naphthofuran:



$$C_{10}H_6\left\{\begin{matrix}[1]O-\\ \\ [2]CH\end{matrix}\right.\!\!>CH \quad\text{and}\quad C_{10}H_6\left\{\begin{matrix}[1]CH\\ \\ [2]O-\end{matrix}\right.\!\!>CH$$

m.p. 7° and 61°, b.p. 283° and 285° (*Stoermer*, Ann. **312**, 237 *ff.*). **Naphtho[1,2-*b*]furan-3(2)-one**, $C_{10}H_6(C_2H_2O_2)$, m.p. 92°, from 2-bromoacetyl-1-acetoxynaphthalene (*Ullmann*, Ber. **30**, 1468). **4,5,4′,5′-Dibenzoöxindigo**, orange-yellow, m.p. 310° (*Fries*, Ann. **442**, 254). **6,7,6′,7′-Dibenzoöxindigo**, brick-red, m.p. 347°.

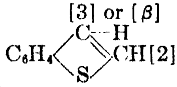
* * * * * * * *

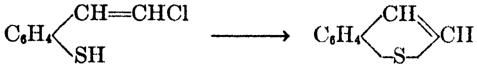
Compounds of the type of **phthalan**, 1,3-*dihydroisobenzofuran*,  are also known (*Willstätter, Veraguth*, Ber. **40**, 965; *Ludwig*, Ber. **40**, 3060; *Nelken, Simonis*, Ber. **41**, 986; *Simonis, Remmert*, Ber. **47**, 2310), but they appear to be unimportant.

6. THIANAPHTHENES (BENZOTHIOPHENES)

This group of compounds contains many useful dyestuffs. Thioindigo red, the sulfur analogue of indigo, was first prepared by *P. Friedländer*; after this discovery the whole field of thianaphthenes was extensively investigated.

The name "thianaphthene" is derived from the close resemblance of the compounds of this class to naphthalenes.

Thianaphthene, *benzothiophene*,  or [α], m.p. 32°, b.p. 221°, picrate m.p. 149°, with an odor like naphthalene, is formed from *o*-mercapto-β-chlorostyrene, which can be isolated only in the form of its xanthogenate (*Gattermann, Lockhart*, Ber. **26**, 2809):



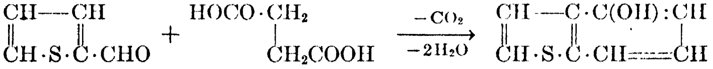
The best preparation is from the easily obtained 3-thianaphthenol by reduction with zinc dust and glacial acetic acid (*Bezdrik, Friedländer, Koeniger*, Ber. **41**, 230). It is present in coal tar and tar from lignite (*Weissgerber, Kruber*, Ber. **53**, 1551). For its separation from naphthalene, with which it is obtained from coal tar, by partial sulfonation, see Ger. Pats. 325712 (1919) and 333156 (1920); for separation by treatment with sodium amide, see Ger. Pat. 350737 (1919) and *Weissgerber, Kruber*, Ber. **53**, 1551. Thianaphthene is also found among the products of many pyrolytic condensations, such as those obtained on heating a mixture of acetylene and hydrogen sulfide at 650° (*Meyer, Meyer*, Ber. **51**, 1571).

Sodium amide converts thianaphthene to a sodium derivative (see above), and ethylmagnesium bromide converts it to a magnesium derivative, ethane being evolved. Thianaphthene and KOH at 300° give *o*-toluenethiol (*Weissgerber, Seidel*, Ber. **60**, 2089). 2,3-*Dihydrothianaphthene*, b.p. 234° (770 mm.), and *o*-ethylbenzenethiol are formed by reduction of thianaphthene with Na and alcohol (*Fricke, Spilker*, Ber. **58**, 1589). For nitration, see p. 59. For spectroscopic data, see *v. Auwers, Kohlhaas*, J.pr. **108**, 321.

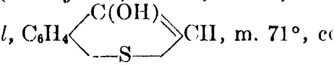
3-**Bromothianaphthene**, b.p. 137° (13 mm.); 2,3-**dibromo-** and 2,3-**dichlorothianaphthene**, m.p. 57.5° and 54° (*Komppa*, J.pr. **122**, 326).

2-**Thianaphthenecarboxylic acid**, m.p. 236°, from the Na or Mg derivative of thianaphthene with CO_2 at 145° (*Weissgerber, Kruber*, Ber. **53**, 1560; Ger. Pat. 341837, 1920); methyl ester, m.p. 72°, b.p. 171° (14 mm.); ethyl ester, m.p. 73°. 3-**Thianaphthenecarboxylic acid**, m.p. 174° (*Komppa*, J.pr. **122**, 322). 2,3-**Thianaphthenedicarboxylic acid**, m.p. 250°, formed as a side-product in the preparation of the 2-carboxylic acid; dimethyl ester, m.p. 91°, b.p. 214° (18 mm.); anhydride, m.p. 171°.

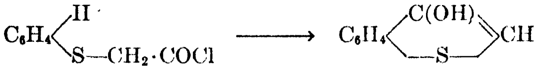
4-**Thianaphthenol**, m.p. 72°, similarly to acetylbenzofuranol (p. 52), is prepared by condensation of thiophenecarboxaldehyde with succinic acid (*Biedermann*, Ber. **19**, 1619):



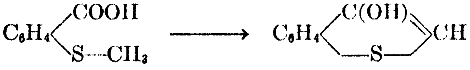
2-**Thianaphthenol**, m.p. 35° (*Weissgerber, Kruber*, Be. **53**, 15 1562).

3-**Thianaphthenol**, *thioindoxyl*,  m. 71°, colorless needles.

It is prepared: (*1*) from 3-hydroxythianaphthene-2-carboxylic acid by decarboxylation (*Friedländer*, Ann. **351**, 408); (*2*) from 3-thianaphtheneamine or its carboxylic acid by boiling in dilute mineral acid; (*3*) from phenylthioglycolic acid by treatment with fuming sulfuric acid or chlorosulfonic acid; this reaction is suitable only for the preparation of substituted 3-thianaphthenols from those phenylthioglycolic acids in which sulfonation is rendered impossible by the presence of substituents; (*4*) from phenylthioglycolic acid chloride and $AlCl_3$, a smooth reaction (Ger. Pat. 197162):



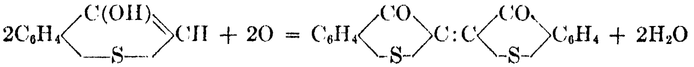
(*5*) from S-methylthiosalicylic acid by fusion with alkali, in the presence of a condensation agent, such as sodium cyanamide or lead sodium (Ger. Pat. 200200):



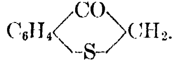
(*6*) by the action of acetoacetic ester and concentrated sulfuric acid on thiosalicylic acid (*Hutchison Smiles*, J. **101**, 570).

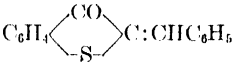
The sulfone of 3-thianaphthenol is prepared from benzoylacetic ester by treatment with fuming sulfuric acid, together with other products (*Arndt, Kirsch, Nachtwey*, Ber. **59**, 1074).

3-Thianaphthenol resembles 1-naphthol in its behavior. It has a similar odor, volatilizes with steam, and couples with diazonium salts, forming azo dyestuffs which are similar to those derived from 1-naphthol. In alkaline solution it oxidizes even in the air, and more readily with potassium ferricyanide, ferric chloride, and the like, to thioindogo red, which is analogous to indoxyl (Ger. Pat. 194237, 1905; Frdl. **VIII**, 1373):

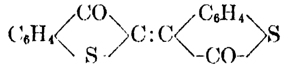


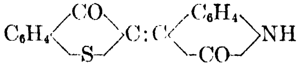
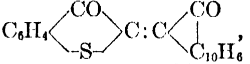
2-Bromo-3-thianaphthenol, m.p. 88°, and **2,2-dibromo-3(2)-thianaphthenone**, m.p. 132°, by bromination of 3-thianaphthenol (*Bezdrik, Friedländer, Koeniger*, Ber. **41**, 227). Both are easily converted to thioindigo red by removal of HBr or 2 Br (*Friedländer*, Mo. **29**, 371).

In many cases 3-thianaphthenol reacts in the desmotropic form as 3(2)-thianaphthenone,  Thus, with aldehydes and ketones it forms colored condensation products, which are called *thioindogenides* from their analogy to the indogenides (p. 70): 2-benzylidene-3(2)-thianaphthenone:

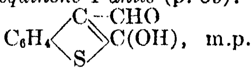


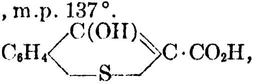
yellow needles, m.p. 127° (*Friedländer*, Mo. **30**, 347). With thianaphthenequinone (p. 59) 3-thianaphthenol condenses to *thioindirubin*,

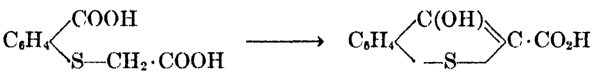


(p. 59), with isatin to *thioindigo scarlet*,  (p. 59), and with acenaphthenequinone to the orange-red 2-(2-*oxo*-1-*acenaphthenylidene*)-3(2)-*thianaphthenone, Ciba scarlet G*, , (*Grob*, Ber. **41**, 3331; *Friedländer*, Mo. **29**, 373). For numerous new thioindigo dyes, see Frdl. **X-XVI**.

With nitrous acid 3-thianaphthenol forms *thianaphthenequinone*-1-*monoxime*, with aromatic nitroso compounds, *thianaphthenequinone*-1-*anils* (p. 59).

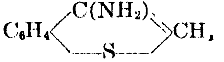
2-Hydroxythianaphthene-3-carboxaldehyde, , m.p. 130°, results from the cleavage of 2-(2-oxo-3-thianaphthenylidene)-pseudoindoxyl (p. 59) with alkali (*Friedländer, Kielbasinski*, Ber. **44**, 3107). **3-Hydroxythianaphthene-2-carboxaldehyde**, m.p. 107°, from 3-thianaphthenol with HCN and HCl (*Krollpfeiffer*, Ann. **462**, 46); phenylhydrazone, m.p. 137°.

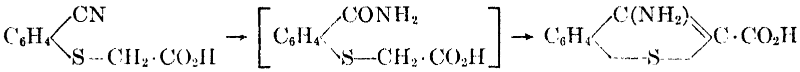
3-Hydroxythianaphthene-2-carboxylic acid, , methyl ester, m.p. 104°, is obtained from *o*-carboxyphenylthioglycolic acid by fusion with KOH or by warming with acetic anhydride and sodium acetate at 40-50° (*Friedländer*, Ann. **351**, 405):



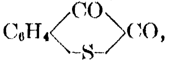
This acid decomposes readily into CO_2 and 3-thianaphthenol, and gives with aldehydes, nitrous acid, *etc.*, the same reaction products as the latter. Oxidation yields thioindigo red.

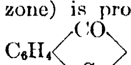
Thianaphthene is converted by nitric acid (d = 1.52) in glacial acetic acid to 3-**nitrothianaphthene**, m.p. 81°. With acid reducing agents the latter gives 3-thianaphtheneamine, with alkaline reducing agents, 2,2′-bisthianaphthene derivatives (*Fries, Hammecke*, Ann. **470**, 1).

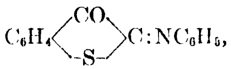
3-Thianaphtheneamine,  oily liquid, acetyl derivative, m.p. 169°, with the characteristic odor of 1-naphthylamine, is prepared by reduction of 3-nitrothianaphthene (see above) or by decarboxylation of 3-**amino-thianaphthene-2-carboxylic acid,** $C_8H_4S(NH_2)CO_2H$, m.p. 146° (dec.), which is obtained by treatment of *o*-cyanophenylthioglycolic acid with dilute alkali or cold concentrated sulfuric acid:

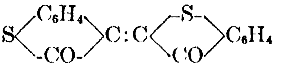


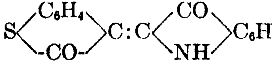
When warmed with dilute mineral acids 3-thianaphtheneamine is transformed into 3-thianaphthenol (*Friedländer*, Ann. **351**, 412; Ger. Pat. 190291).

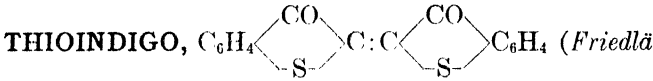
Thianaphthenequinone, 2,3-*dioxodihydrothianaphthene*,  yellow prisms, m.p. 121°, b.p. 247°, is prepared: (*1*) from thianaphthenequinone-2-anil (see below) with dilute mineral acids (Ger. Pat. 214781, 1907; *Pummerer*, Ber. **43**, 1370); (*2*) from thianaphthenequinone-2-oxime (isonitrosothioindoxyl) (see below) by hydrolysis with 50% sulfuric acid or, better, by reduction to 3-hydroxythianaphthene-2-amine and oxidation of the latter with ferric chloride; (*3*) from 2,2-dibromo-3(2)-thianaphthenone (p. 58) by boiling in water or lead acetate solution (*Bezdrik, Friedländer, Koeniger*, Ber. **41**, 234; Ger. Pat. 212782).

Thianaphthenequinone behaves like isatin (p. 74). With thiophene and concentrated H_2SO_4 it turns dark blue. With hydroxylamine and phenylhydrazine it forms thianaphthenequinone-3-oxime, m.p. 186°, and the 3-phenylhydrazone of thianaphthenequinone, m.p. 166°; neither a dioxime nor a di-(phenylhydrazone) is produced. The **thianaphthenequinone-2-oxime,** *isonitrosothioindoxyl*,  m.p. 172° (dec.), obtained from 3-thianaphthenol with nitrous acid, gives a phenylhydrazone, thianaphthenequinone-2-oxime-3-phenylhydrazone, m.p. 154° (Ger. Pat. 213458, 1906). Hydrogen peroxide in ammoniacal solution converts thianaphthenequinone into derivatives of benzisothiazole (*Stollé*, Ber. **58**, 2095).

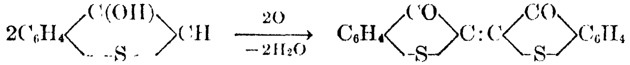
Thionaphthenequinone 2-anil,  m.p. 151°, from 2,2-dibromo-3(2)-thianaphthenone and aniline; *p*-alkylamino- and *p*-dialkylamino-2-anils are obtained by condensation of 3-thianaphthenol with *p*-nitrosoalkylanilines (*Pummerer*, Ber. **43**, 1370). With 3-thianaphthenol, indoxyl, and similar compounds containing reactive methylene groups, thianaphthenequinone condenses, with loss of water, to indigoid dyestuffs, the 3-carbonyl group being the one to enter the reaction: **thioindirubin,** $\Delta^{2,3'}$-*bithianaphthene*-3,2′-*dione*,



red needles, m.p. 206° (*Friedländer*, Mo. **29**, 373); **2-(2-oxo-3-thianaphthenylidene)-pseudoindoxyl,**  (p. 58). The isomeric dyestuffs are obtained by reaction of the same compounds with 2,2-dibromo-3(2)-thianaphthenone or thianaphthenequinone-2-anil (see under thioindigo red).

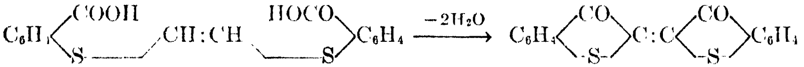
THIOINDIGO,  $C_6H_4<\begin{matrix}CO\\S\end{matrix}>C:C<\begin{matrix}CO\\S\end{matrix}>C_6H_4$ (*Friedländer*, Ber. **39**, 1060; Ann. **351**, 390), the sulfur analogue of indigo, is a vat dye which colors the fiber a dull violet-red, and which is of great technical importance because of its fastness. It crystallizes from nitrobenzene in shiny brown-red needles, which melt over 280° and sublime even below this temperature. At higher temperatures it changes to an orange-red vapor and distills almost undecomposed. Its solutions show a strong yellow-red fluorescence.

Methods of Preparation.—1. Oxidation of 3-thianaphthenol or its carboxylic acid in alkaline solution by the oxygen of the air or, better, by potassium ferricyanide, ferric chloride or the like:



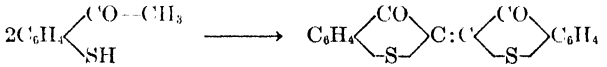
$$2C_6H_4<\begin{matrix}C(OH)\\S\end{matrix}>CH \xrightarrow[-2H_2O]{2O} C_6H_4<\begin{matrix}CO\\S\end{matrix}>C:C<\begin{matrix}CO\\S\end{matrix}>C_6H_4$$

2. Condensation of *s*-bis-(*o*-carboxyphenylmercapto)-ethylene (from dichloroethylene and *o*-mercaptobenzoic acid) with acid condensing agents, such as chlorosulfonic acid (Ger. Pat. 205324, 1907):



$$C_6H_4<\begin{matrix}COOH\\S\end{matrix}>CH:CH<\begin{matrix}HOCO\\S\end{matrix}>C_6H_4 \xrightarrow{-2H_2O} C_6H_4<\begin{matrix}CO\\S\end{matrix}>C:C<\begin{matrix}CO\\S\end{matrix}>C_6H_4$$

3. Oxidation of *o*-acetylbenzenethiol in alkaline solution with the oxygen of the air (Ger. Pat. 198509, 1907):



$$2C_6H_4<\begin{matrix}CO-CH_3\\SH\end{matrix} \longrightarrow C_6H_4<\begin{matrix}CO\\S\end{matrix}>C:C<\begin{matrix}CO\\S\end{matrix}>C_6H_4$$

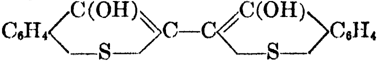
This method is especially useful for the preparation of the valuable alkoxy derivatives of thioindigo red (Ger. Pat. 202632, 1907).

The following methods are only of theoretical interest:

4. Treatment of thianaphthenequinone 2-anil in glacial acetic acid solution with hydrogen sulfide, with separation of sulfur (*Friedländer*, Mo. **29**, 371).

5. Condensation of 2,2-dibromo-3(2)-thianaphthenone or thianaphthenequinone 2-anil with 3-thianaphthenol.

Properties.—Strong oxidation in aqueous media gives thianaphthenequinone (p. 59). Concentrated nitric acid acts on a suspension of thioindigo in glacial acetic acid to form, depending on the temperature, a monosulfoxide or a monosulfone (*Posner*, *Wallis*, Ber. **57**, 1673). Thioindigo is more stable to alkali than the indole indigo, being converted to *thioindirubin* (p. 59) only by boiling alcoholic KOH. 3-Thianaphthenol and thianaphthenequinone are formed as intermediate products in the latter reaction (*Friedländer*, *Sander*, Ber. **57**, 648).

When thioindigo red is treated with zinc dust and alkali or alkaline hydrosulfite solution, a slightly yellow solution results; from this, **thioindigo white,** $C_{16}H_{10}O_2S_2$, is precipitated by acid. This compound is insoluble in water and readily soluble in alkali; in the air it oxidizes to thioindigo red. Since it is also formed by moderate oxidation of 3-thianaphthenol (thioindoxyl) with $FeCl_3$ or NaClO, it must be **bithioindoxyl, 2,2′-bi-3-thianaphthenol,**  $C_6H_4<\begin{matrix}C(OH)\\S\end{matrix}>C-C<\begin{matrix}C(OH)\\S\end{matrix}>C_6H_4$, diacetyl derivative, m.p. 240° (*Friedländer*, Mo. **29**, 372).

Certain generalizations can be made concerning the dyeing properties of a series of technically valuable derivatives of thioindigo, particularly the chloro, alkoxy and alkylmercapto derivatives. Substituents in the 6,6′-position (*p*-position to the carbonyl group) shift the shade toward yellow, while substituents in the 5,5'-position (*p*-position to the S-atom) make it more blue. For light absorption and shade of a number of thioindigo dyes, see *Formanek*, Z.angew.Chem. **41** (1928), 1133.

For the technical preparation of thioindigo dyes, especially of the important 6,6'-dihalogenothioindigos, a procedure depending on a novel method for introducing sulfur into the molecule is in use. The first step consists in the treatment of aromatic primary amines with S_2Cl_2. For the remaining steps, see Ger. Pat. 360690, 1914; Frdl. **XIV**, 908.

A few tricyclic compounds containing a thiophene ring fused on a naphthalene ring are known:

Naphthothiophenes (*benzothianaphthenes*). In this series also the 3-hydroxy and the 2,3-dioxo derivatives are the most important, because of their use in the preparation of indigoid dyestuffs (Swiss Pats. 92688, 93487–9, 1920; Swiss Pats. 102033, 104921, 1922; U. S. Pat. 1492054, 1924; Brit. Pat. 214864, 1923).

Selenindigo, $\Delta^{2,2'}$-*bi-3(2)-selenanaphthenone*, m.p. about 330°, reddish brown crystals from xylene (*Lesser, Weiss*, Ber. **46**, 2653; *Lesser, Schoeller*, Ber., **47** 2292).

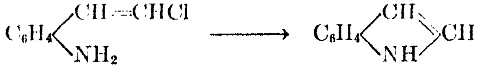
7. INDOLES (BENZOPYRROLES)

The most important compounds belonging to this group were found among the decomposition products of *indigo*; their close relation to indigo was uncovered by the fundamental research of *Adolf v. Baeyer*. Hence the name *indole* was given to the basic bicyclic ring system. More recently the indoles have been investigated for their physiological significance, being products of pancreatic digestion and of the decomposition of albumin.

INDOLE (for formula and numbering, see p. 51), m.p. 52°, b.p. 245° (dec.), occurs in coal tar, and is separated from the fraction boiling between 240° and 260° in the form of its solid, easily decomposed alkali derivatives by heating with KOH or sodium amide (*Weissgerber*, Ber. **43**, 3520).

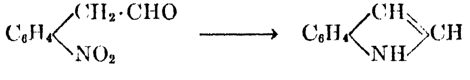
Indole is prepared: *1.* By distillation of its derivatives containing oxygen, such as oxindole (p. 72) and indigo (p. 78) with zinc dust; or, better, from indoxyl or its carboxylic acid by reduction with sodium amalgam or zinc dust and alkali (*Vorländer, Apelt*, Ber. **37**, 1134; Ger. Pat. 152683, 1902). Small yields of indole are obtained when a mixture of aniline vapor and acetylene is passed through an incandescent tube (*Majima, Unno, Ono*, Ber. **55**, 3854).

2. By condensation of various *o*-amino derivatives of benzene, or by reduction of the *o*-nitro compounds; for example, by treatment of *o*-amino-β-chlorostyrene with sodium alcoholate, a reaction analogous to those used to prepare benzofuran (p. 51) and thianaphthene (p. 56) (*Lipp*, Ber. **17**, 1067):



$$C_6H_4\left\langle\begin{matrix}CH{=}CHCl\\NH_2\end{matrix}\right. \longrightarrow C_6H_4\left\langle\begin{matrix}CH\\NH\end{matrix}\right\rangle CH$$

Also from *o*-nitrophenylacetaldehyde or *o*-nitrocinnamic acid by reduction:



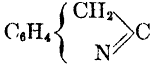
$$C_6H_4\left\langle\begin{matrix}CH_2\cdot CHO\\NO_2\end{matrix}\right. \longrightarrow C_6H_4\left\langle\begin{matrix}CH\\NH\end{matrix}\right\rangle CH$$

The formation of indole from phenylglycine, $C_6H_5NH\cdot CH_2\cdot COOH$, and calcium formate is a similar reaction (*Mauthner, Suida*, Mo. **11**, 373; Ger. Pat. 213713, 1908).

3. The formation of indole when alkylated anilines and tetrahydroquinoline, particularly *cumidine* and *methyl-o-toluidine*, are distilled in an incandescent tube depends on *ortho*-condensations (*Carrasco, Padoa*, Atti accad.Lincei [5] **15**, II, 729).

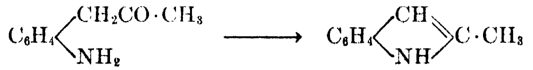
4. Indole is formed, together with skatole, from albuminates in the pancreatic fermentation or on fusion with alkali. It is found in *jasmine* and *orange blossom oil* (*Hesse*, Ber. **32**, 2612), in the essential oil from *Robinia pseudacacia* [*Elze*, Chem.-Ztg. **34** (1910), 814] and in the oil of numerous other flowers (*Sack*, Pharm.Weekbl. **48**, 307).

Properties.—Indole crystallizes from water in shiny platelets; it possesses a characteristic odor resembling naphthylamine, and is volatile with steam. Its solutions and its vapor color a pine shaving moistened with HCl and alcohol brick-red (characteristic reaction of the pyrrole nucleus, see p. 29). Indole is only slightly basic, and is quickly resinified by acids. As in pyrrole, the imine hydrogen can be replaced by potassium or sodium. With methylmagnesium iodide it reacts to form methane and indolylmagnesium iodide, $C_8H_6N{\cdot}MgI$, which gives 1-indolecarboxylic acid with CO_2, 3-alkylindoles with alkyl iodides, and 3-indolyl ketones with acid chlorides. For the mechanism of these reactions, see *Putochin*, Ber. **59**, 1987; J.Russ. Phys.-Chem.Soc. **58** (1926), 119; *Majima, Hoshino*, Proc.Imp.Acad. Tokyo **3** (1927), 339; C. **1927, II,** 1957. With picric acid, indole forms a compound which crystallizes in red needles, and with sodium bisulfite it forms a hydrosulfonic acid (*Hesse*, Ber. **32**, 2615). With chloroform and alkali, indole behaves like pyrrole (p. 30), giving both 3-indolecarboxaldehyde and, by an enlargement of the ring, 3-chloroquinoline (*Ellinger*, Ber. **39**, 2516). When heated with KOH at 200°, the indole ring is opened, and *o*-toluidine results (*Fromm*, Ber. **60**, 2090). Treatment with active oxygen or sulfomono peracid converts indole into indigo.

Some derivatives of indole are derived from a desmotropic form, *pseudoindole* or *indolenine*,  $C_6H_4\left\{\begin{matrix}CH_2\\ N\end{matrix}\right\rangle CH$; *cf.* trimethylindolenines (p. 63), nitroso-2-alkylindoles (p. 66) and diazoindoles (p. 66) (*Angeli, Morelli*, Atti accad.Lincei [5] **17, I,** 697).

1-**Nitrosoindole**, m.p. 172°, from indole and sodium nitrite, seems to have a doubled formula (*Zatti, Ferratini*, G. **21, II,** 23; Ber. **23**, 2299); 1-**Acetylindole**, b.p. 152°, is prepared, together with other products, by heating indole with acetic anhydride (*Zatti, Ferratini*, Ber. **23**, 1359, 2296). 1-**Benzoylindole**, m.p. 68°, from the sodium derivative of indole and benzoyl chloride (*Weissgerber*, Ber. **43**, 3523), is converted by permanganate in acetone solution to N-benzoylanthranilic acid (*Weissgerber*, Ber. **46**, 656).

1. **HOMOLOGOUS INDOLES** are prepared: (*a*) By ring-closure of *o*-aminobenzene derivatives:



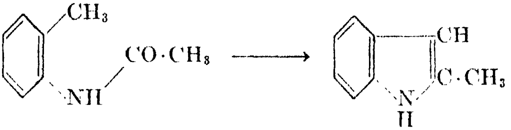
$$C_6H_4\left\langle\begin{matrix}CH_2CO{\cdot}CH_3\\ NH_2\end{matrix}\right. \longrightarrow C_6H_4\left\langle\begin{matrix}CH\\ NH\end{matrix}\right\rangle C{\cdot}CH_3$$

o-Aminobenzyl methyl ketone 2-Methylindole

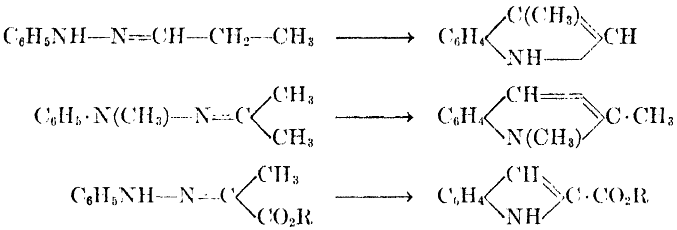
o-Aminodesoxybenzoin condenses to 2-phenylindole, and *o*-methylamino-β-chlorostyrene condenses to N-methylindole.

(*b*) By heating aniline or its derivatives with compounds containing the group —CO·CHCl—. Intermediate products form which contain the grouping ArN:C·CH·NHAr. Aniline with chloroacetone gives 2-methylindole, with α-bromoacetophenone, 2-phenylindole and with β-bromolevulinic acid, 2,3-dimethylindole (CO_2 being split in the reaction). For the course of this reaction, see *Bischler*, Ber. **25**, 2860; *Bischler, Fireman*, Ber. **26**, 1336; *Japp, Murray*, Ber. **26**, 2638; *Hell, Cohén*, Ber. **37**, 867. Benzoin and aniline condense to 2,3-diphenylindole, and benzoin and *m*-phenylenediamine, to a tetraphenylated benzodipyrrole [*Japp, Meldrum,* J. **75** (1899), 1044; *Richards,* J. **97** (1910), 977].

(*c*) By treatment of N-acyl-*o*-toluidines with sodium amide, 2-alkylindoles being formed (*Verley,* Bull. [4] **35,** 1039):



(*d*) An important reaction for the formation of alkylindoles consists in the condensation of the phenylhydrazones of aldehydes, ketones, and ketoacids by heating them with hydrochloric acid, alcoholic sulfuric acid, or zinc chloride (*Fischer,* Ber. **19,** 1563):



$$C_6H_5NH{-}N{=}CH{-}CH_2{-}CH_3 \longrightarrow C_6H_4\left\langle\begin{matrix}C(CH_3)\\NH\end{matrix}\right\rangle CH$$

$$C_6H_5\cdot N(CH_3){-}N{=}C\left\langle\begin{matrix}CH_3\\CH_3\end{matrix}\right. \longrightarrow C_6H_4\left\langle\begin{matrix}CH{=}\\N(CH_3)\end{matrix}\right\rangle C\cdot CH_3$$

$$C_6H_5NH{-}N{=}C\left\langle\begin{matrix}CH_3\\CO_2R\end{matrix}\right. \longrightarrow C_6H_4\left\langle\begin{matrix}CH\\NH\end{matrix}\right\rangle C\cdot CO_2R$$

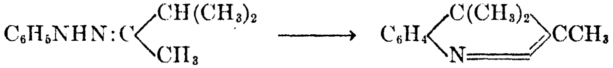
For an interpretation of the reaction mechanism, see *Bodforss,* Ber. **58,** 775.

The phenylhydrazones are usually prepared from the corresponding carbonyl compounds, but in some cases the phenylhydrazine group is introduced by coupling aliphatic 1,3-dicarbonyl compounds with benzene diazonium chloride [*cf. Kalb, Schweizer, Schimpf,* Ber. **59,** 1858; *Keimatsu, Sugasawa,* J.Pharm.Soc. Japan **48** (1928), 63, 101; C. **1928, II,** 49, 1881].

Pyruvic acid and *as*-alkylphenylhydrazines react smoothly when warmed with dilute HCl, H_2SO_4, or H_3PO_4 to form 1-alkylindolecarboxylic acids. The phenylhydrazones of β-oxo carboxylic acids, such as acetoacetic ester, usually give pyrazolones, although some, especially the *as*-alkylphenylhydrazones, form indoles when heated with concentrated H_2SO_4 [*Walker,* Am.Chem.J. **16** (1894), 430].

In the case of aldehydes and ketones which contain a tertiary methine group next to the carbonyl group, the condensation, in the presence of alcoholic $ZnCl_2$, hydriodic acid or stannous chloride and hydrochloric acid, takes a somewhat different course. The phenylhydrazones yield derivatives of pseudoindole or indolenine (p. 62), while the *as*-alkylphenylhydrazones give derivatives of dihydroindole, or *indoline* (*Plancher,* Ber. **31,** 1488; Atti accad. Lincei [5] **9, I,** 115; *Brunner,* Ber. **31,** 1948; Mo. **21,** 156; *cf.* also *indolone,* p. 72):

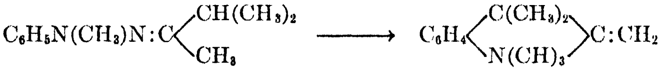
1.



$$C_6H_5NHN{:}C\left\langle\begin{matrix}CH(CH_3)_2\\CH_3\end{matrix}\right. \longrightarrow C_6H_4\left\langle\begin{matrix}C(CH_3)_2\\N{=}\end{matrix}\right\rangle CCH_3$$

Trimethylpseudoindole,
Trimethylindolenine

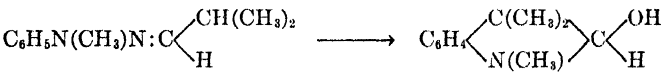
2.



$$C_6H_5N(CH_3)N{:}C\left\langle\begin{matrix}CH(CH_3)_2\\CH_3\end{matrix}\right. \longrightarrow C_6H_4\left\langle\begin{matrix}C(CH_3)_2\\N(CH)_3\end{matrix}\right\rangle C{:}CH_2$$

Trimethylmethyleneindoline

3.

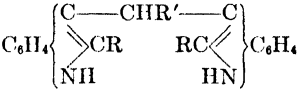


$$C_6H_5N(CH_3)N{:}C\left\langle\begin{matrix}CH(CH_3)_2\\H\end{matrix}\right. \longrightarrow C_6H_4\left\langle\begin{matrix}C(CH_3)_2\\N(CH_3)\end{matrix}\right\rangle C\left\langle\begin{matrix}OH\\H\end{matrix}\right.$$

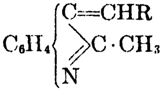
Trimethylindolinol

A number of methylindoles have been isolated from coal tar (*Kruber,* Ber. **59,** 2752).

Properties.—The indoles substituted by alkyl groups in the pyrrole nucleus generally have a fecal odor, and distill undecomposed. The phenylindoles are odorless and nonvolatile. The homologues of indole are more stable to acid than indole itself, and can be precipitated from solution in concentrated acid by the addition of water. With picric acid they form compounds crystallizing in red needles. Most indoles, with the exception of 2,3-dialkylindoles and the indolecarboxylic acids, give the pine-shaving reaction. When fused with caustic potash, the alkylindoles, like the alkylpyrroles, are oxidized to indolecarboxylic acids. With acid anhydrides, nitrous acid, and diazonium compounds, the indoles react as the pyrroles (p. 28 *ff.*) do, being substituted in the pyrrole ring by acyl, isonitroso, and benzeneazo groups. Two mols of indole and of indoles substituted in the 2- or 3-position condense with 1 mol aldehyde (*Weiss, Fastmann,* Mo. **47,** 727), to form compounds of the type:

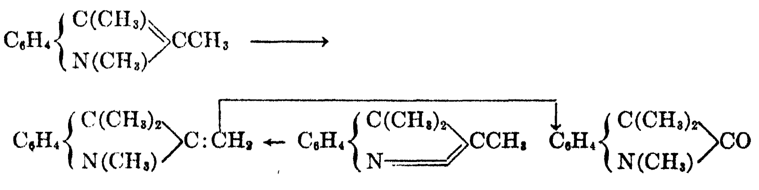


(either the 2- or the 3-hydrogen atom can take part in this reaction) (*Renz, Loew,* Ber. **36,** 4326; *Feuerstein, Brass,* Ber. **37,** 822; *Renz,* Ber. **37,** 1221; *v. Walther, Clemen,* J.pr. **61,** 249). These condensation products can be oxidized to dyestuffs resembling fuchsin, the *rosindoles,* which are also obtained directly by condensation of the corresponding indoles with benzoyl chloride in the presence of $ZnCl_2$ (*Fischer, Wagner,* Ber. **20,** 815). 4,4′-Diaminobenzophenone (Vol. III, p. 519) reacts similarly to the aldehydes, forming red to violet dyes (Ger. Pat. 128660, 1901). 2-*Methylindole* condenses with aldehydes also to give compounds of the type:

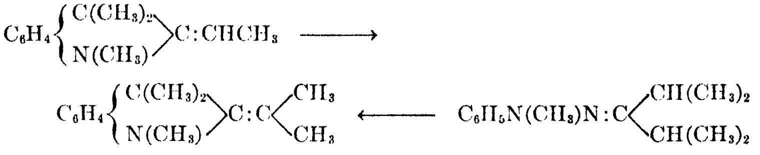


(*Freund, Lebach,* Ber. **36,** 308; **38,** 2640). In its desmotropic form (*cf.* p. 62) 2-methylindole also reacts with aromatic nitroso compounds (*Angeli, Morelli,* Atti accad.Lincei [5] **17,** I, 697).

The behavior of indole and alkylated indoles on exhaustive alkylation with alkyl iodides is rather complex. For example, indole and 2-methylindole, when treated with methyl iodide, are first completely methylated in the pyrrole ring, and then add another methyl group; this product is proved to be 1,3,3-*trimethyl-2-methyleneindoline* by synthesis (see p. 63), by oxidation to trimethyloxindole (p. 72), and by conversion to *trimethylpseudoindole* (see p. 63), from which it can be regenerated by methylation (*Plancher,* Ber. **31,** 1488; Gazz. **28,** II, 333; *Piccinini,* Atti accad.Lincei [5] **7,** I, 358):



The methylenetrimethylindoline is converted by further methylation to *ethylidene-* and *isopropylidenetrimethylindolines*, which are also obtained from ethyl isopropyl ketone and diisopropyl ketone methylphenylhydrazones:

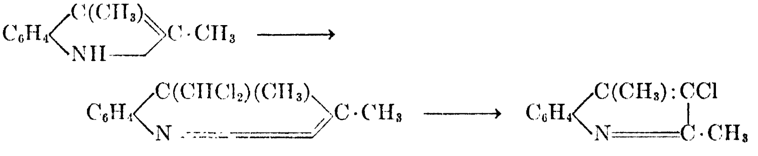


$$C_6H_4\left\{\begin{matrix}C(CH_3)_2\\N(CH_3)\end{matrix}\right.>C{:}CHCH_3 \longrightarrow$$

$$C_6H_4\left\{\begin{matrix}C(CH_3)_2\\N(CH_3)\end{matrix}\right.>C{:}C\begin{matrix}CH_3\\CH_3\end{matrix} \longleftarrow C_6H_5N(CH_3)N{:}C\begin{matrix}CH(CH_3)_2\\CH(CH_3)_2\end{matrix}$$

The ethylation of methylated, ethylated or phenylated indoles follows a similar course. Isomerization caused by wandering of the alkyl groups has also been observed (*Plancher*, Gazz. 28, II, 374; Atti accad.Lincei [5[**9**, I, 115; *ibid.* **11**, II, 182).

When alkylindoles are warmed with chloroform and sodium alcoholate, the pyrrole ring, as in pyrrole (p. 30) and indole (p. 62), is enlarged, so that, in addition to the indole aldehydes, 3-chloroquinolines are also formed. 2,3-Dimethylindole yields first *3-dichloromethyl-2,3-dimethylpseudoindole*, which is converted by warming with sodium ethylate to *3-chloro-2,4-dimethylquinoline* (*Plancher, Carrasco*, Atti accad.Lincei [5] **14**, I, 162):



$$C_6H_4\begin{matrix}C(CH_3)\\NH\end{matrix}>C\cdot CH_3 \longrightarrow$$

$$C_6H_4\begin{matrix}C(CHCl_2)(CH_3)\\N=\!=\!=\end{matrix}>C\cdot CH_3 \longrightarrow C_6H_4\begin{matrix}C(CH_3){:}CCl\\N=\!=\!=C\cdot CH_3\end{matrix}$$

1-Methylindole,* b.p. 239°, **1-ethylindole**, b.p. 247°, **1-allylindole**, b.p. 252° (*Michaelis, Luxembourg*, Ber. **26**, 2175), and **1-phenylindole**, b.p. 327°, are prepared from their carboxylic acids by decarboxylation. N-Methyl- and N-ethylindole are oxidized by bromine and sodium hydroxide solution to methyl- and ethylisafin (p. 75). **1-Benzoylindole**, m.p. 68°, b.p. 213° (16 mm.), from the sodium derivative of indole and benzoyl chloride (*Weissgerber*, Ber. **43**, 3523).

2-Methylindole, methylketole, m.p. 59°, b.p. 268°, from *o*-aminobenzyl methyl ketone, from the phenylhydrazone of acetone (see above) and from coal tar (*Kruber*, Ber. **59**, 2752), resembles indole in odor and behavior. Oxidation in fused alkali gives the 2-carboxylic acid, while oxidation with permanganate splits the pyrrole ring, producing N-acetylanthranilic acid. When passed through an incandescent tube, it rearranges, like 2-methylpyrrole (p. 31), to *quinoline* (*Pictet*, Ber. **38**, 1949). With chloroform and sodium alcoholate it gives *3-chloroquinaldine* (*Magnanini*, Ber. **21**, 1940).

3-Methylindole, skatole, m.p. 95°, b.p. 265°, occurs in coal tar (in traces) and in human feces, together with a little indole; it is formed in the putrefaction or alkali fusion of albumins, and is best synthesized from propylenephenylhydrazine (see above). It has a penetrating fecal odor. With chloroform and sodium alcoholate it gives *3-chlorolepidine* (*Ellinger, Flamand*, Ber. **39**, 4388). **3-Ethylindole**, m.p. 43°, from indolylmagnesium iodide and ethylmagnesium iodide, and from the phenylhydrazone of *n*-butyraldehyde (*Plancher, Carrasco*, Atti accad.Lincei [5] **14**, II, 677). **4-Methylindole**, liquid, b.p. 267° (*Kruber*, Ber. **62**, 2877). **5-Methylindole**, m.p. 60°, and **7-methylindole**, m.p. 85°, are isolated from coal tar (*Kruber*, Ber. **59**, 2753, 2759).

2,3-Dimethylindole, m.p. 106°, from the phenylhydrazone of methyl ethyl ketone (*Fischer*, Ann. **236**, 128). **1,2,3-Trimethylindole**, b.p. 280° (see above).

2-Phenylindole, m.p. 187°, is obtained from the phenylhydrazone of acetophenone, from *o*-nitrodesoxybenzoin, from α-bromoacetophenone and aniline, and from **3-phenylindole**, m.p. 89°, by heating with zinc chloride at 170° (*Fischer, Schmidt*, Ber. **21**, 1811). Rearrangements like that of 3-phenylindole also take place in methylphenylindoles (*Ince*, Ann. **253**, 35). **2,3-Diphenylindole**, m.p. 124°, from desylaniline or the phenylhydrazone of desoxybenzoin (*Bischler*,

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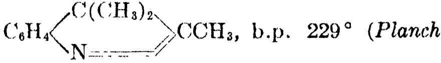
* For the numbering of substituents, see p. 51.

Fireman, Ber. 26, 1341). **2-(2′-Thienyl)indole,** m.p. 162°, and **2-(1-naphthyl)indole,** m.p. 180°, are prepared from the phenylhydrazones of thienyl and naphthyl methyl ketones (*Pschorr, Kuhtz,* Ber. 38, 217).

2,3,3-Trimethylpseudoindole,

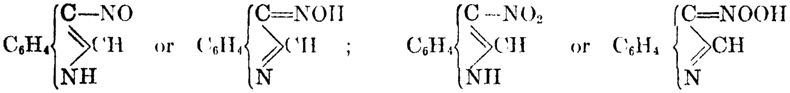


$C_6H_4\left\langle\begin{matrix}C(CH_3)_2\\ N{=\!=}\end{matrix}\right\rangle CCH_3$

b.p. 229° (*Plancher, Bettinelli,* Gazz. 29, I, 106), from the phenylhydrazone of methyl isopropyl ketone (see above). **2,3-Dimethyl-3-ethylpseudoindole,** b.p. 243°, from the phenylhydrazone of 3-methyl-2-pentanone (*cf. Plancher,* Atti accad.Lincei [5] 9, I, 115). **2-Methyl-3,3-diethylpseudoindole** is prepared by ethylation of 2-methylindole.

2. **HALOGEN DERIVATIVES.** Chlorine is introduced into the heterocyclic ring of indoles by the action of sulfuryl chloride on their solutions in ether, by treatment of 1-benzoylindoles with chlorine (*Weissgerber,* Ber. 46, 652) or by the reaction of oxindole or 3-hydroxyoxindole with PCl_5. The position of the halogen in the monochloro derivative has not been determined. ***Py*-Monochloroindole,** m.p. 94°; **monobromoindole,** m.p. 67° (*Weissgerber,* Ber. 46, 653); **2,3-dichloroindole,** m.p. 104°; **3-iodoindole,** m.p. 72° (*Pauly, Gundermann,* Ber. 41, 4005).

3. **NITROSO, NITRO, AND BENZENEAZO DERIVATIVES.** When treated with nitrous acid, from $NaNO_2$ and glacial acetic acid or, better, from amyl nitrite and sodium alcoholate, and with nitric acid, from ethyl nitrate and sodium in ether, only those indoles which are unsubstituted in a 3-position react immediately. Thus, indole, 2-methylindole, 2-phenylindole, and the like are converted to nitroso and nitro derivatives, which also exist in the tautomeric forms of isonitroso and isonitro compounds:

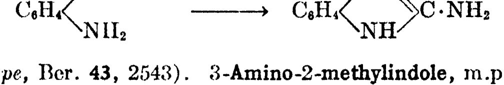


$C_6H_4\begin{cases}C{-}NO\\ \quad\rangle CH\\ NH\end{cases}$ or $C_6H_4\begin{cases}C{=}NOH\\ \quad\rangle CH\\ N\end{cases}$; $C_6H_4\begin{cases}C{-}NO_2\\ \quad\rangle CH\\ NH\end{cases}$ or $C_6H_4\begin{cases}C{=}NOOH\\ \quad\rangle CH\\ N\end{cases}$

The nitroso group is oxidized to the nitro group by permanganate. **3-Nitrosoindole,** dec. 170° (*Madelung,* Ann. 405, 87, 91). **3-Nitroso-2-methylindole,** m.p. 198° (dec.). **3-Nitroso-2-phenylindole,** m.p. 250°. **3-Nitroindole,** yellow needles, m.p. 210°, is also obtained from 3-nitroindole-2-carboxylic acid (see below), which is proof of its constitution; further nitration with nitric acid in glacial acetic acid converts it to **2,3-dinitroindole,** dec. 260°. **3-Nitro-2-methylindole,** yellow scales, m.p. 248°. **3-Nitro-2-phenylindole,** m.p. 239–241°. The nitrosophenylindole is oxidized by chromic acid to benzoylanthranilic acid, the nitromethylindole by permanganate to 3-nitroindole-2-carboxylic acid.

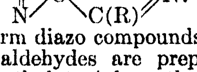
The indoles substituted in the 2-position also react smoothly with diazonium compounds: **3-phenylazo-2-methylindole,** m.p. 115°; **3-phenylazo-2-phenylindole,** m.p. 166°.

4. **AMINOINDOLES. 2-Aminoindole,** lustrous prisms, diacetyl derivative, m.p. 142°, is prepared by the intramolecular rearrangement of *o*-aminobenzyl cyanide when warmed with alcoholic sodium ethylate:



$$C_6H_4\left\langle\begin{matrix}CH_2\cdot CN\\ NH_2\end{matrix}\right. \longrightarrow C_6H_4\left\langle\begin{matrix}CH\\ NH\end{matrix}\right\rangle C\cdot NH_2$$

(*Pschorr, Hoppe,* Ber. 43, 2543). **3-Amino-2-methylindole,** m.p. 113°, and **3-amino-2-phenylindole,** m.p. 180°, from the corresponding nitroso compounds (see above). When treated with nitrous acid the 3-aminoindoles form yellow diazo compounds of remarkable stability, which appear to be derived from the desmotropic form of indole (p. 62):



$\begin{matrix}N\\ \|\\ N\end{matrix}\rangle C\left\langle\begin{matrix}C_6H_4\\ C(R)\end{matrix}\right\rangle N$.

1-Aminoindole and 1-ethyl-3-aminophenylindole do not form diazo compounds with nitrous acid.

5. **ALDEHYDES.** Indolecarboxaldehydes are prepared by treatment of indoles with chloroform and sodium ethylate (*cf.* synthesis of hydroxybenzaldehydes, Vol. III, p. 343), together with 3-chloroquinolines; a better method is the condensation of 3-indolylmagnesium bromide and formic acid ester [*Majima,*

Kotake, Ber. **55**, 3865; *Putochin*, J.Russ.Phys.Chem.Soc. **58** (1926), 119]. Several indolecarboxaldehydes have been obtained by the action of HCN and HCl on indoles (*Fischer, Pistor*, Ber. **56**, 2313). **3-Indolecarboxaldehyde,** m.p. 195°, is formed by the oxidation of tryptophan (see below) with $FeCl_3$. Oxime, m.p. 200°. Permanganate oxidizes it to 3-indolecarboxylic acid. When warmed with dilute mineral acids, it forms a red dye. It is used in the synthesis of several indole derivatives having side-chains in the 3-position (see tryptophan, and *Majima, Kotake*, Ber. **58**, 2037). **2-Methylindole-3-carboxaldehyde,** m.p. 198°, is obtained from 2-methylindole with amyl formate and sodium ethylate, or with HCN and HCl (*Fischer, Pistor*, Ber. **56**, 2313).

6. KETONES. Indolyl ketones are prepared by the reaction of indolylmagnesium iodides (p. 62) with acid chlorides, or by the treatment of indoles with cyanides and gaseous HCl (*Fischer, Pistor*, Ber. **56**, 2313). **3-Indolyl methyl ketone,** $C_8H_6N\cdot COCH_3$, m.p. 189°, and **3-indolyl ethyl ketone,** m.p. 158°, are formed by the alkali fusion of 3-indolecarboxylic acid. **3-Indolyl phenyl ketone,** m.p. 170°. **2-Methylindolyl methyl ketone,** m.p. 195° (*Fischer, Pistor*, Ber. **56**, 2313).

7. CARBOXYLIC ACIDS. Indolecarboxylic acids are obtained: (*a*) from the phenylhydrazones of pyruvic acid and its derivatives (p. 63) by reactions similar to those used in the preparation of pyrrolecarboxylic acids; (*b*) from indoles by heating with Na and CO_2; (*c*) from alkylindoles by fusion with alkali (*Ciamician, Magnanini*, Ber. **21**, 1925). When heated alone or with calcium hydroxide, the indolecarboxylic acids decompose into indoles and CO_2.

1-Indolecarboxylic acid, $C_8H_6N\cdot CO_2H$, m.p. 108° (dec.), from indolylmagnesium iodide and CO_2 (*Oddo, Sessa*, Gazz. **41**, I, 234; *cf. Majima, Kotake*, Ber. **55**, 3865).

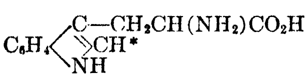
2-Indolecarboxylic acid, m.p. 200° (dec.), from the phenylhydrazone of pyruvic acid, from 2-methylindole by alkali fusion, and from tetrahydrocarbazole (p. 87) by fusion with alkali. It is also formed by reduction of *o*-nitrophenylpyruvic acid with zinc dust and glacial acetic acid; reduction with sodium amalgam gives 1-hydroxyindolecarboxylic acid (*Reissert*, Ber. **30**, 1045). When heated with acetic anhydride 2-indolecarboxylic acid forms an imide-anhydride analogous to pyrocoll (p. 37) (*Anderlini*, Ber. **22**, 2503). For derivatives of the acid such as the hydrazide and azide, see *Piccinini, Salmoni*, Gazz. **32**, I, 246.

3-Indolecarboxylic acid, m.p. 218° (dec.), from skatole by alkali fusion, from indole with Na and CO_2 (*Weissgerber*, Ber. **43**, 3526) or from indolylmagnesium bromide and CO_2 (*Majima, Kotake*, Ber. **55**, 3865). It does not form an imide-anhydride (*Zatti, Ferratina*, Ber. **23**, 2296). Indigo in yields up to 38% is obtained from 3-indolecarboxylic acid in alkaline solution with air containing ozone, while not a trace of the dye is formed by the isomeric 2-carboxylic acid (*Weissgerber*, Ber. **46**, 657). Its nitrile, m.p. 178°, is prepared by the action of sodium and formic acid ester on *o*-aminobenzyl cyanide, and by treatment of 3-indolealdoxime with acetic anhydride (*Pschorr, Hoppe*, Ber. **43**, 2548). **1,2-Dimethylindole-3-carboxylic acid,** m.p. 200°, from the methylphenylhydrazone of acetoacetic ester:

$$C_6H_5N(CH_3)\cdot N{:}C(CH_3)\cdot CH_2\cdot CO_2R$$

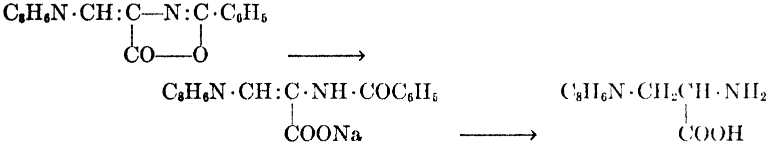
3-Indoleacetic acid, *α-skatolecarboxylic acid*, m.p. 165°, from the phenylhydrazone of *β*-formylpropionic acid ester (Vol. I, p. 461), $C_6H_5NHN{:}CHCH_2CH_2COOC_2H_5$, according to method *d* (p. 63) (*Ellinger*, Ber. **37**, 1801). It occurs with indole, skatole, and **3-indolepropionic acid,** m.p. 134°, in the putrefaction products of albumins. The indolepropionic acid is prepared from the phenylhydrazone of *γ*-formylbutyric acid ester, $C_6H_5NH\cdot N{:}CH\cdot CH_2\cdot CH_2\cdot CH_2CO_2C_2H_5$ (*Ellinger*, Ber. **38**, 2884; *Kalb, Schweizer, Schimpf*, Ber. **59**, 1858). Both indoleacetic acid and indolepropionic acid are formed in the decomposition of tryptophan.

***l*-TRYPTOPHAN,** *α-amino-3-indolepropionic acid, 3-indolylalanine,*



$$C_6H_4\left\langle\begin{array}{l} C{-}CH_2CH(NH_2)CO_2H \\ \quad\rangle CH^* \\ NH \end{array}\right.$$

m.p. about 289°, is produced in the hydrolysis of most proteins. It derives its name from its occurrence in the tryptic digestion of proteins, where its presence is shown by an intense red-violet color reaction to bromine (the tryptophan reaction). It was first obtained in a pure condition in 1901. Although tryptophan accounts for only 1 to 3% of the structure of most proteins, it is a vital amino acid. Ferric chloride oxidizes it to 3-indolecarboxaldehyde (see above), from which it can be obtained synthetically. Like benzaldehyde (Vol. III, p. 268), 3-indolecarboxaldehyde condenses with hippuric acid, sodium acetate and acetic anhydride, forming *α-benzoylamino-3-indoleacrylic acid lactone;* after saponification of the lactone group with sodium hydroxide, the product is reduced with sodium and alcohol, which also splits off the benzoyl group, leaving racemic tryptophan, m.p. 285° (*Ellinger,* Ber. **40,** 3029; *Ellinger, Flamand,* Z.physiol.Chem. **55,** 8):

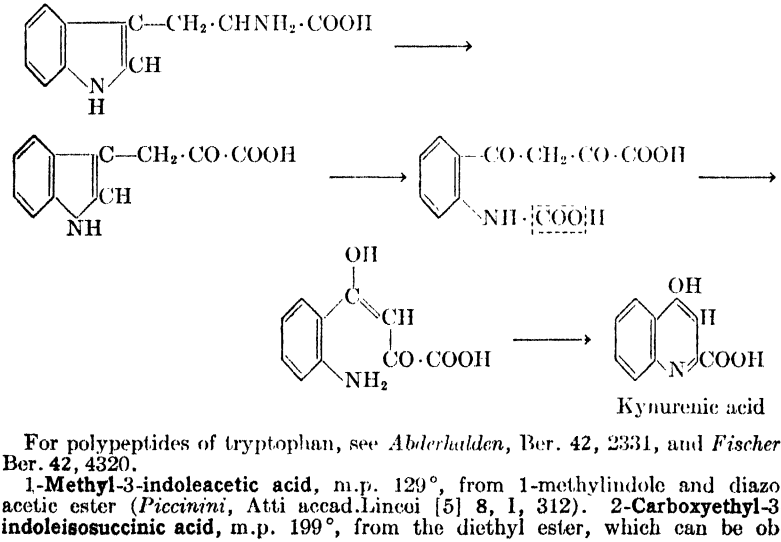


$$\begin{array}{l} C_8H_6N\cdot CH\!:\!C{-}N\!:\!C\cdot C_6H_5 \\ \quad\;\; CO{-}O \end{array} \longrightarrow \begin{array}{l} C_8H_6N\cdot CH\!:\!C\cdot NH\cdot COC_6H_5 \\ \qquad\qquad\; COONa \end{array} \longrightarrow \begin{array}{l} C_8H_6N\cdot CH_2CH\cdot NH_2 \\ \qquad\qquad\; COOH \end{array}$$

An analogous synthesis of *dl*-tryptophan starts from hydantoin instead of hippuric acid (*Majima, Kotake,* Ber. **55,** 3859).

Properties.—Besides the reaction with bromine mentioned above, tryptophan gives a whole series of color reactions, most of which involve the pyrrole ring. A weak hydrochloric acid solution of tryptophan, containing formaldehyde, turns blue to red-violet on addition of concentrated sulfuric acid. The reaction is made more sensitive (1:125,000) by using dimethylaminobenzaldehyde [*Komm,* Z.physiol.Chem. **156,** 35; *Lieben, Popper,* Biochem.Z. **173,** 455], glyoxylic acid (*Edlbacher,* Z.physiol.Chem. **105,** 240) or vanillin (*Blanchetière,* C.r. **180,** 2072) in place of formaldehyde. With ninhydrin (triketohydrindenehydrate) tryptophan gives the characteristic blue-violet coloring of the α-amino acids (see Vol. I, p. 439, and *Riffart,* Biochem.Z. **131,** 78).

When exposed to the action of the bacteria of putrefaction, tryptophan is decarboxylated to 3-*(2-aminoethyl)-indole,* $C_8H_6N\cdot CH_2\cdot CH_2NH_2$, m.p. 146° (m.p. 114°?, *Majima, Hoshino,* Ber. **58,** 2045), which can also be prepared from the phenylhydrazone of γ-aminobutyraldehyde by heating with $ZnCl_2$ (*Ewins,* J. **99,** 270). In the dog's body *l*-tryptophan is transformed into *kynurenic acid* or 4-hydroxyquinoline-2-carboxylic acid. This reaction seems to take place in these steps (*Ellinger,* Z.physiol.Chem. **109,** 261):

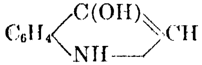


Kynurenic acid

For polypeptides of tryptophan, see *Abderhalden,* Ber. **42,** 2331, and *Fischer,* Ber. **42,** 4320.

1-Methyl-3-indoleacetic acid, m.p. 129°, from 1-methylindole and diazoacetic ester (*Piccinini,* Atti accad.Lincei [5] **8,** I, 312). **2-Carboxyethyl-3-indoleisosuccinic acid,** m.p. 199°, from the diethyl ester, which can be obtained by treatment of 2-indolepropionic acid with methoxymethylmalonic ester (*Maurer, Moser,* Z.physiol.Chem. **161**, 131).

8. *Py*(1, 2 or 3)-**HYDROXYINDOLES. Indoxyl,** *3-hydroxyindole,*



$$C_6H_4\left\langle\begin{matrix}C(OH)\\NH\end{matrix}\right\rangle CH$$

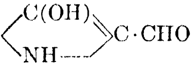
yellow crystals, m.p. 85°, is formed by the decarboxylation of indoxylic acid when warmed in water (*Vorländer, Drescher,* Ber. **35**, 1701). Indoxyl is synthesized directly from N-methylanthranilic acid, $CH_3NHC_6H_4COOH$, and from phenylglycine, $C_6H_5NHCH_2COOH$, by fusion with sodium amide (*cf.* indigo syntheses, p. 79). The indigo-forming constituent of the indigo plant, *indican* (*vegetable indican*), $C_{14}H_{17}O_6N \cdot 3H_2O$, m.p. 58°, anhydrous, m.p. 180° (constitution: *Macbeth, Pryde,* J. **1923**, I, 1627) is a glucoside of indoxyl [*Hazewinkel,* Chem.-Ztg. **24** (1900), I, 1294; *Hoogewerff, Ter Meulen,* Rec. **19**, 166; *Ter Meulen* Rec. **28**, 339]. The solution of indoxyl in water has a yellow fluorescence. Indoxyl is rather unstable and resinifies readily. It dissolves in concentrated hydrochloric acid with a red color. In alkaline solution it oxidizes in the air to *indigo;* the oxidation is accelerated by ferric chloride:

$$\underset{\text{Indoxyl}}{2C_8H_7ON} + O_2 = \underset{\text{Indigo}}{(C_8H_5ON)_2} + 2H_2O$$

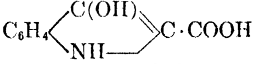
When warmed with potassium pyrosulfate indoxyl forms the potassium salt of **indoxylsulfuric acid,** $C_8H_6N \cdot O \cdot SO_3K$, which is found in the urine of plant-eating animals and in human urine after the ingestion of indole (*urine indican*); when warmed with acids this salt regenerates indoxyl, which forms indigo on treatment in the cold with a little $FeCl_3$ (test for indoxylsulfuric acid in urine).

Acetic anhydride reacts with free indoxyl to give N-**acetylindoxyl,** m.p. 136°, but in alkaline solution **O-acetylindoxyl,** $C_8H_6N(OCOCH_3)$, m.p. 126°, is formed. **O,N-Diacetylindoxyl,** m.p. 82°, from N-acetylindoxyl, or from anthranilinoacetic acid, with acetic anhydride (*Vorländer, v. Pfeiffer,* Ber. **52**, 325).

In many cases indoxyl reacts in the tautomeric form as 3(2)-**indolone** (see p. 70).

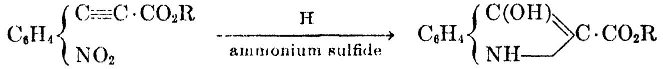
Indoxylaldehyde,  $C_6H_4\left\langle\begin{matrix}C(OH)\\NH\end{matrix}\right\rangle C \cdot CHO$, lustrous needles, which decompose at 160°, is formed by fusion of indigo with KOH, together with anthranilic acid, with which it condenses in the presence of acids to *chrysanilic acid,* $C_8H_6ON \cdot {-}CH{:}NC_6H_4CO_2H$ (*Friedländer, Schwenk,* Ber. **43**, 1971).

INDOXYLIC ACID, *3-hydroxyindole-2-carboxylic acid,*



$$C_6H_4\left\langle\begin{matrix}C(OH)\\NH\end{matrix}\right\rangle C \cdot COOH$$

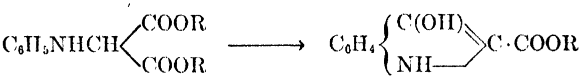
m.p. 123° (dec.), is prepared from its ethyl ester, m.p. 116°, by fusion with NaOH (*Forrer,* Ber. **17**, 976). The ester is obtained: *1.* By reduction of *o*-nitrophenylpropiolic acid ester, or of its rearrangement product, isatogen-2-carboxylic acid ester (see p. 74), with ammonium sulfide:



$$C_6H_4\begin{cases}C{\equiv}C \cdot CO_2R\\NO_2\end{cases}\xrightarrow[\text{ammonium sulfide}]{H} C_6H_4\begin{cases}C(OH)\\NH\end{cases}\!\!\Big\rangle C \cdot CO_2R$$

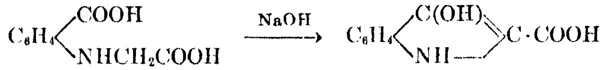
Indoxanthinic acid ester has been observed to be an intermediate product of this reaction (Ger. Pat. 17656, 1881); this oxidizes to indoxylic acid ester.

2. By condensation of anilinomalonic acid ester at 260–265° (*Blank,* Ber. **31**, 1816):



$$C_6H_5NHCH\left\langle\begin{matrix}COOR\\COOR\end{matrix}\right. \longrightarrow C_6H_4\begin{cases}C(OH)\\NH\end{cases}\!\!\Big\rangle C \cdot COOR$$

3. By heating N-*o*-carboxyphenylglycine with caustic alkali, a method of technical importance (*Vorländer, v. Pfeiffer,* Ber. **52**, 325):

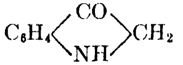


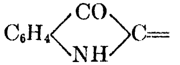
The esters of N-*o*-carboxyphenylglycine are condensed to indoxylic acid esters by sodium ethylate solution. The N-acyl and N-alkyl derivatives react even more readily; the latter give N-alkylindoxylic acid esters (*Vorländer*, Ber. **35**, 1683; *Vorländer, Mumme*, Ber. **35**, 1699).

When warmed with concentrated sulfuric acid, indoxylic acid esters give a quantitative yield of *indigotin*-5,5′-*disulfonic acid.* Indoxylic acid esters are converted to indigo by heating with alkali while air is blown in, and to a dimolecular imide-anhydride (like indole-2-carboxylic acid, p. 67) by heating at 240–260° (*Conrad, Reinbach*, Ber. **35**, 524).

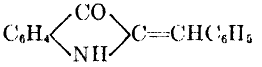
The phenol character of indoxylic acid esters is shown in their solubility in alkalis, from which solutions they can be reprecipitated with CO_2. Ethyl iodide reacts with salts of indoxylic acid esters to form **O-ethylindoxylic acid esters,** $C_8H_5(OC_2H_5)NCO_2R$, which are hydrolyzed to **O-ethylindoxylic acid,** m.p. 160°, by barium hydroxide; this acid loses CO_2 when heated, leaving **O-ethylindoxyl,** $C_8H_6(OC_2H_5)N$, which resembles indole in odor and behavior. When warmed with HCl O-ethylindoxylic acid gives *indoxyl*; when treated with nitrous acid, it forms *pseudoisatoxime* (p. 76).

In many reactions indoxyl and indoxylic acid yield products which are derived from the tautomeric 3(2)-indolone (A). The divalent group (B) is called the

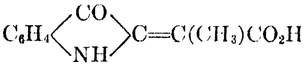
(A) 

 (B)

pseudoindoxyl or *indogen* group, and the compounds formed by the condensation of indoxyl or indoxylic acid with aldehydes, ketones and ketone carboxylic acids are called *indogenides* (*Baeyer*, Ber. **16**, 2197):



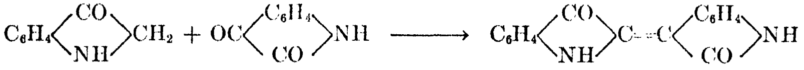
Indogenide of benzaldehyde



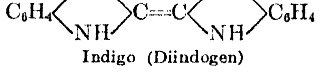
Indogenide of pyruvic acid

The indogenides of protocatechualdehyde and of aminobenzaldehyde are dyestuffs [*Noelting*, Bull.soc.ind.Mulhouse **72** (1902), 236].

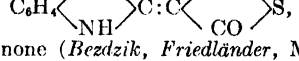
The reaction of isatin and indoxyl (*Forrer*, Ber. **17**, 976) produces the indogenide **indirubin** (p. 84):

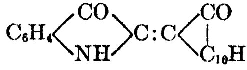


which is isomeric with indigo. Indigo is formed by the oxidation of indoxyl (p. 69) or by condensation of indoxyl with isatin-α-chloride (2-chloro-3-pseudoindolone), and therefore may be regarded as diindogen:



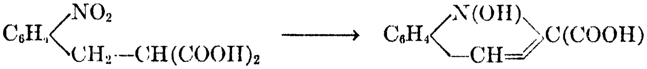
Indigo (Diindogen)

By a similar reaction **3-thianaphthene-2-indole-indigo,** 2-**(2-oxo-3-thianaphthenylidene)-pseudoindoxyl,** , is obtained from indoxyl and thianaphthenequinone (*Bezdzik, Friedländer*, Mo. **29**, 375), and 1-**acenaphthene-2-indole indigo,** 2-**(2-oxo-1-acenaphthenylidene)-pseudoindoxyl,**



from indoxyl and acenaphthenequinone (*Grob*, Ber. 41, 3332).

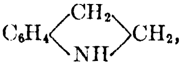
1-Hydroxyindole-2-carboxylic acid, m.p. 159° (dec.), is prepared by boiling *o*-nitrobenzylmalonic acid with sodium hydroxide solution:

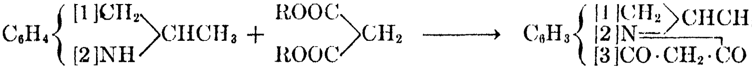


$$C_6H_4\left\langle\begin{matrix}NO_2\\ CH_2{-}CH(COOH)_2\end{matrix}\right. \longrightarrow C_6H_4\left\langle\begin{matrix}N(OH)\\ CH=\end{matrix}\right\rangle C(COOH)$$

and by the reduction of *o*-nitrophenylpyruvic acid with sodium amalgam. The acid is readily reduced to 2-indolecarboxylic acid. It is oxidized by permanganate to *o*-azoxybenzoic acid, by chromic acid to isatin. The hydroxy group on the N is easily acylated and alkylated. In the presence of calcium hypochlorite, sodium peroxide and the like, 1-hydroxyindole-2-carboxylic acid rearranges to **indoxin,** a blue dyestuff similar to indigo, but soluble in alkali and unstable; when the solution of this dye in concentrated sulfuric acid is diluted and allowed to stand in the air, indigo precipitates in good yield (*Reissert,* Ber. **29,** 639; **30,** 1045, 1052).

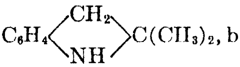
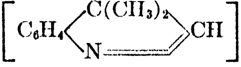
1-Hydroxy-2-phenylindole, $C_8H_5N(C_6H_5)(OH)$, m.p. 175°, is obtained by the action of concentrated sulfuric acid on the oxime of benzoin (*Angeli, Angelico,* Atti accad.Lincei [5] **15,** II, 761).

HYDROINDOLES. **Indoline,** *2,3-dihydroindole,*  $C_6H_4\left\langle\begin{matrix}CH_2\\ NH\end{matrix}\right\rangle CH_2$, b.p. 221°, is prepared from indole by electrolytic reduction, but more readily from 1-methylindoline by heating with HI and phosphorus (*v. Braun,* Ber. **45,** 1285). **1-Benzoylindoline,** m.p. 119°; **nitrosoindoline,** m.p. 84°. Alkylindoles are reduced with greater ease than indole itself, either electrolytically or with Sn and HCl. The hydroindoles differ greatly from indole in their behavior, resembling, rather, the alkylated anilines. With silver sulfate the dihydroindoles are oxidized to indoles (*Kann, Tafel,* Ber. **27,** 827). **1-Methylindoline,** b.p. 216° (*Wenzing,* Ann. **239,** 246). **2-Methylindoline,** b.p. 227°, is resolved into optically active components by bromocamphorsulfonic acid. When heated with HI and phosphorus, 2-methylindoline gives *o*-propylaniline. With malonic acid ester it forms a tricyclic condensation product (*Bamberger, Sternitzki,* Ber. **26,** 1298):

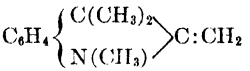


$$C_6H_4\left\{\begin{matrix}[1]CH_2\\ [2]NH\end{matrix}\right\rangle CHCH_3 + \begin{matrix}ROOC\\ ROOC\end{matrix}\rangle CH_2 \longrightarrow C_6H_3\left\{\begin{matrix}[1]CH_2\rangle CHCH_3\\ [2]N=\!=\!\urcorner\\ [3]CO{\cdot}CH_2{\cdot}CO\end{matrix}\right.$$

2,3-Dimethylindoline, b.p. 229°.

2,2-Dimethylindoline,  $C_6H_4\left\langle\begin{matrix}CH_2\\ NH\end{matrix}\right\rangle C(CH_3)_2$, b.p. 210°, is obtained by distillation of *o*-isopropylaminobenzyl alcohol. The isomeric 3,3-**dimethylindoline,** m.p. 35°, b.p. 228°, is prepared by reduction of 3,3-dimethyloxindole (p. 72) or, better, by reduction of the condensation product of isobutylidenephenylhydrazine, the trimolecular *3,3-dimethylpseudoindole,*  $\left[C_6H_4\left\langle\begin{matrix}C(CH_3)_2\\ N=\!=\!=\end{matrix}\right\rangle CH\right]_3$ (*Brunner,* Mo. **18,** 115).

1,3,3-*Trialkyl-2-alkylideneindolines,* such as **trimethylmethyleneindoline,**

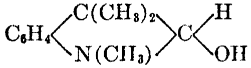


$$C_6H_4\left\{\begin{matrix}C(CH_3)_2\\ N(CH_3)\end{matrix}\right\rangle C{:}CH_2$$

b.p. 129° (21 mm.), and **1-phenyl-3,3-dimethyl-2-methyleneindoline,** b.p. 208° (52 mm.), are prepared from the *as*-alkylphenylhydrazones of certain ketones, and by exhaustive alkylation of indoles (see p. 64). **1,3,3-Trimethyl-2-benzylideneindoline,** m.p. 93°, from 1,3,3-trimethylindolone and benzylmagnesium chloride (*Brunner,* Ber. **38,** 1359). Oxidation converts them to indolones (p. 72).

Octahydroindole, *perhydroindole,* b.p. 185°, chloroplatinate m.p. 173°, is formed by catalytic hydrogenation with platinum black and hydrogen. Very intense hydrogenation (Ni and H_2 in an autoclave) causes a break in the ring, producing *o*-ethylhexahydroaniline (*Willstätter, Seitz, v. Braun,* Ber. **58,** 385; *v. Braun, Bayer,* Ber. **58,** 387).

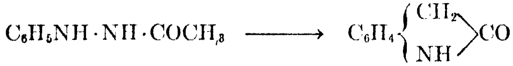
Derivatives of indoline containing oxygen.—Indolinols and indolones are prepared from phenylhydrazones (*cf.* p. 63): **1,3,3-trimethyl-2-indolinol,**



$$C_6H_4\left\langle\begin{matrix}C(CH_3)_2\\N(CH_3)\end{matrix}\right\rangle C\left\langle\begin{matrix}H\\OH\end{matrix}\right.$$

m.p. 95°, and **1-phenyl-3,3-dimethyl-2-indolinol,** m.p. 125°, are obtained from the *as*-phenylmethylhydrazone and the diphenylhydrazone of isobutyraldehyde with alcoholic hydriodic acid or stannous chloride and hydrochloric acid. When warmed with hydrochloric acid these compounds lose a molecule of water and rearrange to trimethyl- or phenyldimethylindole (*Brunner,* Mo. **21,** 156). **1,3,3-Trimethyl-2-phenyl-2-indolinol,** m.p. 102°, from 1,3,3-trimethyl-2-indolinol with C_6H_5MgBr (*Jenisch,* Mo. **27,** 1223).

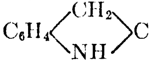
The oxo derivatives of indoline are more important than the hydroxy derivatives. The oxindols, or 2(3)-indolones, may also be considered as lactams of *o*-amino-α-toluic acid and its homologues. The oxindoles can be prepared by heating acylphenylhydrazides with calcium hydroxide, a reaction analogous to the Fischer indole synthesis (p. 63) (*Brunner,* Mo. **18,** 95, 527; *cf.* Ger. Pat. **218727,** 1908):

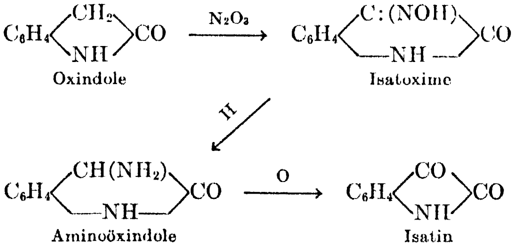


$$C_6H_5NH\cdot NH\cdot COCH_3 \longrightarrow C_6H_4\left\{\begin{matrix}CH_2\\NH\end{matrix}\right\rangle CO$$

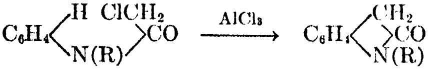
Propionyl-, butyryl-, isobutyryl- and phenacetylphenylhydrazide and propionyl- and isobutyrylmethylphenylhydrazide react similarly: **3-Methyloxindole,** *atroxindole,* m.p. 123°. **3-Ethyloxindole,** m.p. 102°. **3-Phenyloxindole,** m.p. 183°. **3-Isopropyloxindole,** m.p. 106° (*Schwarz,* Mo. **24,** 568). **3,3-Dimethyloxindole,** m.p. 151°. **1,3,3-Trimethyloxindole,** m.p. 47°, b.p. 265°, is formed by oxidation of the corresponding indolinol (see above) or of trimethylalkylindeneindoline (p. 63).

The following compounds are important because of their relation to indigo:

1. **Oxindole,** 2(3)-*indolone,*  $C_6H_4\left\langle\begin{matrix}CH_2\\NH\end{matrix}\right\rangle CO$, m.p. 127°, is prepared from acetylphenylhydrazide with calcium hydroxide (see above). It was first obtained by reduction of 3-hydroxyoxindole, to which it reverts when exposed to the air while damp. For this reason it reduces ammoniacal silver solution. It is the lactam of *o*-aminophenylacetic acid, and therefore can also be obtained by reduction of *o*-nitrophenylacetic acid (*cf. Neber,* Ber. **55,** 826). With N_2O_3 oxindole forms isatoxime (p. 75); the latter can be reduced to **aminoöxindole,** which oxidizes to isatin:

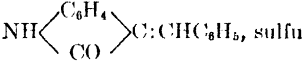


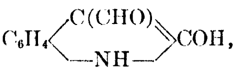
Oxindole and N-alkyloxindoles are formed from the chloroacetyl derivatives of aromatic amines when they are heated with $AlCl_3$ at 160–180° (*Stollé,* Ber. **47,** 2120; J.pr. **105,** 137):

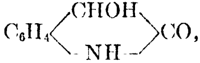
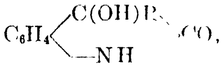


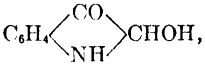
$$C_6H_4\left\langle\begin{matrix}H\ ClCH_2\\N(R)\end{matrix}\right\rangle CO \xrightarrow{AlCl_3} C_6H_4\left\langle\begin{matrix}CH_2\\N(R)\end{matrix}\right\rangle CO$$

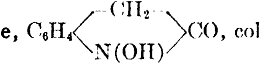
Oxindole and its N-alkyl derivatives condense with aldehydes and ketones, splitting off water and forming colored compounds which are isomeric with the indogenides derived from indoxyl, and are therefore known as *isoindogenides*. Oxindole is readily converted through the 3-isonitroso or the 3,3-dibromo derivative to isatin (*Stollé*, J.pr. **105**, 137).

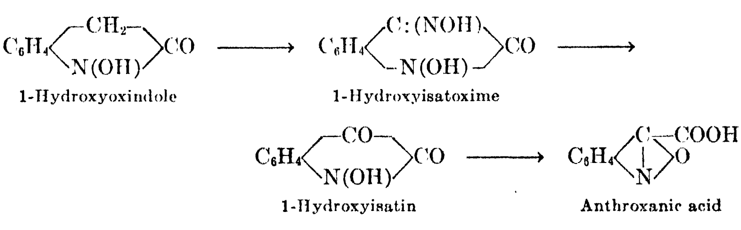
3-Benzylideneoxindole,  $\mathrm{NH}\left\langle\begin{matrix}C_6H_4\\ CO\end{matrix}\right\rangle C{:}CHC_6H_5$, sulfur-yellow needles, m.p. 176°. **Isoindigo,** isomeric with indigo and indirubin, is prepared from oxindole and isatin (p. 84).

Oxindolecarboxaldehyde,  $C_6H_4\left\langle\begin{matrix}C(CHO)\\ —NH—\end{matrix}\right\rangle COH$, yellowish needles, m.p. 213°, is formed together with thiosalicylic acid by the fission of thioindigo scarlet (p. 77) with alkali (*Friedländer, Kielbasinski*, Ber. **44**, 3101).

2. **3-Hydroxyoxindole,** *dioxindole*,  $C_6H_4\left\langle\begin{matrix}CHOH\\ NH\end{matrix}\right\rangle CO$, m.p. 168°, the lactam of *o*-aminomandelic acid, is obtained from *o*-nitromandelic acid, or from isatin by reduction with zinc dust and acetic acid (*Heller*, Ber. **37**, 938). Oxidation converts it to isatin and isatyde (p. 75). 3-Alkyl- and 3-aryl-3-hydroxyoxindoles,  $C_6H_4\left\langle\begin{matrix}C(OH)R\\ —NH\end{matrix}\right\rangle CO$, are prepared by treatment of isatin with organomagnesium compounds (*Kohn*, Mo. **31**, 747). A series of 3-hydroxyoxindoles substituted in the benzene nucleus are produced by heating aromatic primary or secondary amines with mesoxalic acid esters, the 3-carboxylic acid ester being formed first [*Martinet*, Ann.chim. [9] **11** (1919), 15].

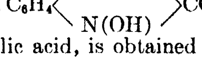
2-Hydroxypseudoindoxyl, *2-hydroxy-3(2)-indolone*,  $C_6H_4\left\langle\begin{matrix}CO\\ NH\end{matrix}\right\rangle CHOH$, isomeric with 3-hydroxyoxindole, is called *indoxanthine*. **2-Hydroxypseudoindoxylcarboxylic acid ethyl ester,** m.p. 107° (not sharp), is formed by mild oxidation of 2-indoxylcarboxylic acid ester in acetone solution with $FeCl_3$ (*Baeyer*, Ber. **15**, 775). This ester is rearranged by a cold solution of sodium carbonate to *3-hydroxyoxindole-3-carboxylic acid ester*, m.p. 152° (*Kalb*, Ber. **44**, 1459).

3. **1-Hydroxyoxindole,**  $C_6H_4\left\langle\begin{matrix}CH_2\\ N(OH)\end{matrix}\right\rangle CO$, colorless rhombic plates, acetyl derivative, m.p. 101°, is prepared by reduction of *o*-nitrophenylacetic acid with zinc dust and sulfuric acid. With nitrous acid it forms **1-hydroxyisatoxime,** m.p. 223°; this, when oxidized and then reduced, gives **1-hydroxyisatin,** which rearranges in acid or alkaline media to the isomeric anthroxanic acid (*Reissert*, Ber. **41**, 3921). For the preparation of 1-hydroxyisatin from *o*-nitrobenzoyl chloride and diazomethane, see *Arndt*, Z.angew.Chem. **40** (1927), 1099.

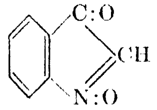


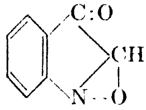
1-Hydroxyoxindole 1-Hydroxyisatoxime

1-Hydroxyisatin Anthroxanic acid

4. **1,3-Dihydroxyoxindole,** *trioxindole*,  $C_6H_4\left\langle\begin{matrix}CH(OH)\\ N(OH)\end{matrix}\right\rangle CO$, m.p. 172° (dec.) the anhydride of *o*-hydroxylaminomandelic acid, is obtained by reduction of *o*-nitromandelic acid with zinc dust and ammonia. When heated by itself or warmed with acetic anhydride it is converted into isatin by loss of a molecule of water; on careful oxidation with permanganate it forms 1-hydroxyisatin (*Heller*, Ber. **42**, 470).

5. The **isatogens,** which are related both to isatin and to indoxyl, are derived from a parent compound, *isatogen*, which has not yet been prepared (formulas I and II):

I 

 II

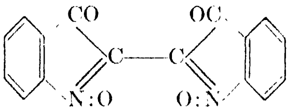
The 2-carboxylic acid ester was first prepared by *A. v. Baeyer*, by the action of concentrated sulfuric acid on *o*-nitrophenylpropiolic acid ester. For its formula, see under isatin.

Isatogen derivatives are also obtained under milder conditions by exposure of the pyridine solution of *o*-nitrophenylpropiolic acid ester to light. By a similar reaction in pyridine solution 2-nitrotolan (2-nitrodiphenylacetylene) is converted to 2-phenylisatogen (*Pfeiffer*, Ann. **411**, 72).

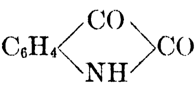
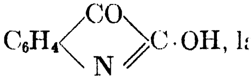
The isatogens resemble quinones, precipitating I_2 from an acidified potassium iodide solution. On reduction they yield indoxyl derivatives; *3-pseudoindolones* have been isolated as intermediate products (*Ruggli, Bolliger*, Helv. **4**, 626). The isatogencarboxylic acid esters are converted to isatin by alkali. When gaseous HCl is led into the alcoholic solution of the isatogens, which is usually red, yellow isomers, *isoisatogens*, are formed; these correspond to formula II (see above) (*Ruggli*, Ber. **52**, 1; *Ruggli, Bolliger*, Helv. **4**, 626).

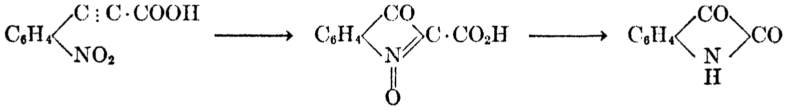
2-Phenylisatogen, m.p. 187°, orange-red; **isatogen-2-carboxylic acid ethyl ester**, m.p. 112°, **methyl ester**, m.p. 201° (*Pfeiffer*, Ann. **411**, 149).

Diisatogen, m.p. 287° (dec.), is prepared from di-(*o*-nitrophenyl)biacetylene by treatment with alkali (*v. Baeyer*) or by irradiation in chloroform solution (*Ruggli, Bolliger*, Helv. **4**, 626). It is converted to indigo by reducing agents.



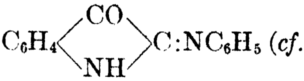
Diisatogen

6. **Isatin,**  $C_6H_4{<}\begin{matrix}CO\\ NH\end{matrix}{>}CO$ lactam form, tautomeric with  $C_6H_4{<}\begin{matrix}CO\\ N\end{matrix}{>}C\cdot OH$, lactime form, m.p. 201°, orange-red prisms, was first prepared by oxidation of *indigo* with nitric acid (*Erdmann*, J.pr. **24**, 11; *Laurent*, J.pr. **25**, 434). Other oxidizing agents such as $KMnO_4$ or CrO_3 can also be used in the presence of water. Isatin is also obtained from *oxindole* and *3-hydroxyoxindole* by oxidation, from *1,3-dihydroxyoxindole* by loss of water and from *o-nitrophenylpropiolic acid* with alkali. In the last reaction *isatogenic acid* (2-carboxy-3-pseudoindolone N-oxide) is formed first, by a rearrangement, and this compound yields isatin by loss of CO_2:



$$C_6H_4{<}\begin{matrix}C:C\cdot COOH\\ NO_2\end{matrix} \longrightarrow C_6H_4{<}\begin{matrix}CO\\ \underset{\underset{O}{\parallel}}{N}\end{matrix}{>}C\cdot CO_2H \longrightarrow C_6H_4{<}\begin{matrix}CO\\ \underset{H}{N}\end{matrix}{>}CO$$

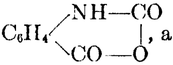
If a reducing agent is added to the alkaline solution of *o*-nitrophenylpropiolic acid, *indigo* is formed instead of isatin (p. 78).

The easily synthesized isatin 2-anil,  $C_6H_4<\begin{matrix}CO\\NH\end{matrix}>C{:}NC_6H_5$ (*cf.* p. 76) gives isatin when heated with dilute mineral acids (Ger. Pat. 113979, 1899).

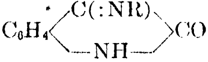
Oxanilide chloride, $C_6H_5N{:}CCl\cdot CCl{:}NC_6H_5$, is converted to isatin by warming with concentrated H_2SO_4 (Ger. Pat. 193633, 1907). The formation of N-alkylisatins from alkyl-aryl- or diaryloxamic acid chlorides, $C_6H_5\cdot N(R)\cdot CO\cdot COCl$, with $AlCl_3$ proceeds smoothly (*Stollé*, Ber. **46**, 3915).

Properties.—*1.* Isatin is one of the classic examples of a tautomeric substance (see Vol. I, p. 48). According to the reaction conditions, it can form derivatives of its lactam form or of its lactime form (see above). The absorption curve of isatin in alcoholic solution is parallel to that of its N-methyl derivative; it may therefore be assumed that isatin in the solid state and in alcoholic solution (contrary to the conclusion of *A. v. Baeyer*) exists in the lactam form.

2. Isatin dissolves in aqueous alkali with a red-violet color, since the alkali salts of isatin have the lactime structure (see above) (*Hantzsch*, Ber. **54**, 1257). After several minutes in the cold, and more rapidly on heating, the solutions become brighter, due to the formation of the alkali salts of *o-aminophenylglyoxylic acid*, or *isatic acid*, by fission of the pyrrole ring.

3. Oxidation of isatin with chromic acid in glacial acetic acid gives *isatoic acid anhydride*,  $C_6H_4<\begin{matrix}NH-CO\\ \qquad|\\CO-O\end{matrix}$, and with nitric acid, *nitrosalicylic acid.*

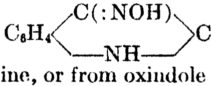
4. Reduction with ammonium sulfide gives first *isatyde*, $C_{16}H_{12}O_4$ (constitution: *Hantzsch*, Ber. **54**, 1257; *Reissert, Hessert*, Ber. **57**, 964), then 3-hydroxyoxindole and oxindole.

5. With ammonia and primary amines isatin forms compounds of the general formula  $C_6H_4<\begin{matrix}C(:NR)\\NH\end{matrix}>CO$, which are called *imesatins;* these revert to isatin and amines when treated with alkali (*cf.* isatinanil). *o*-Phenylenediamine and isatin yield *indophenazine* (*Schunck, Marchlewski*, Ber. **29**, 194; *Marchlewski*, Ber. **29**, 1030; *Korczynski, Marchlewski*, Ber. **35**, 4331; *Haslinger*, Ber. **41**, 1444).

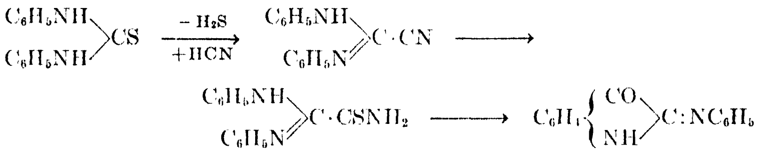
6. Isatin condenses with benzene hydrocarbons, phenols and the like, splitting off a water molecule. With thiophene it gives a blue dyestuff, *indophenin* (constitution, p. 25); similar products are formed from furan and pyrrole (p. 30 and *Liebermann, Krauss*, Ber. **40**, 2492).

N-Benzoylisatin, m.p. 206°; **N-acetylisatin,** m.p. 141°; **N-methylisatin,** m.p. 134°; **N-ethylisatin,** m.p. 95°, by treatment of the alkali salts of isatin with benzoyl chloride, acetic anhydride, methyl iodide, and ethyl iodide. **N-Phenylisatin,** m.p. 136° (*Friedländer, Kunz*, Ber. **55**, 1605), is converted to 9-*acridinecarboxylic acid* by heating with an excess of sodium hydroxide; this rearrangement also takes place with other N-arylisatins.

7. Derivatives of the tautomeric lactime form are obtained from the silver salt of isatin: **O-methylisatin,** m.p. 102° (*Hantzsch*, Ber. **54**, 1243), and **O-ethylisatin,** m.p. 88° (?), 52° (*Hantzsch*, Ber. **55**, 3190), by reaction of the silver salt with methyl iodide and ethyl iodide. The silver salt of isatin and benzoyl chloride react together with water to form *isatoid*, m.p. 178°, a condensation product containing two molecules of isatin (*Hantzsch*, Ber. **58**, 685).

8. Isatin also forms two *isomeric isonitroso derivatives*: isatoxime and isosatoxime. **Isatoxime,**  $C_6H_4<\begin{matrix}C(:NOH)\\NH\end{matrix}>CO$, m.p. 202° (dec.), is prepared from isatin with hydroxylamine, or from oxindole with N_2O_3 (p. 72); on reduction it gives aminooxindole, which can be oxidized to isatin. The silver salt of isatoxime and ethyl iodide give a mono- and a diethyl ether, from which isatin can be formed after saponification. **Pseudoisatoxime,** $C_6H_4\left\langle\begin{matrix}CO\\NH\end{matrix}\right\rangle C{=}NOH$, m.p. 200° (dec.) (synthesis: *Wieland, Gmelin,* Ber. **41,** 3512), is obtained from O-ethylindoxylic acid with N_2O_3 (p. 76); with ethyl iodide this also gives a monoethyl and a diethyl derivative, $C_6H_4\left\langle\begin{matrix}CO\\NH\end{matrix}\right\rangle C{:}NOC_2H_5$ and $C_6H_4\left\langle\begin{matrix}-CO-\\N(C_2H_5)\end{matrix}\right\rangle C{:}NOC_2H_5$, of which only the first can be converted to isatin. Reduction of N-ethylisatin ethyl oxime gives N,N′-*diethylindigo* (p. 84 and *Baeyer,* Ber. **16,** 2201). N-Acetylisatin and hydroxylamine form a **dioxime** (*Kozak,* Anz.Akad.Wiss.Krakau **1909,** 628; **C. 1909, II,** 987). **3-Isatin semicarbazone** (*Marchlewski,* Ber. **29,** 1030). **2-Isatin semicarbazone,** m.p. 228° [*Rupe, Apotheker,* Helv. **9** (1927), 1049]. **3-Isatin phenylhydrazone,** m.p. 211°, from isatin and phenylhydrazine; the isomeric **2-isatin phenylhydrazone,** m.p. 236°, is obtained from O-methylisatin with phenylhydrazine, or from indoxyl and benzenediazonium chloride (*Heller,* Ber. **40,** 1298).

9. There are two isomeric isatin anils: 3-*isatin anil,* $C_6H_4\left\langle\begin{matrix}C(:NC_6H_5)\\—NH—\end{matrix}\right\rangle CO$, golden yellow prisms, m.p. 221°, and **2-isatin anil,** which exists in two modifications, yellow-brown flakes and violet prisms, m.p. 126°, corresponding to the lactam and the lactime form of isatin: $C_6H_4\left\langle\begin{matrix}CO\\NH\end{matrix}\right\rangle C{:}NC_6H_5$ and $C_6H_4\left\langle\begin{matrix}CO\\N\end{matrix}\right\rangle\!\!\!/\,C{\cdot}NHC_6H_5$. When heated, the former rearranges to the latter. Benzoylation of 2-isatin anil gives two benzoyl derivatives, m.p. 173° and 131° (*Callow, Hope,* J. **1929,** 1191). 2-Isatin anil is prepared by reacting isatin chloride (see preceding reference) or O-methylisatin with aniline, or from indoxyl or indoxylic acid with nitrosobenzene (*Pummerer, Goettler,* Ber. **42,** 4269). The starting material for its technical preparation is diphenylthiourea, which is desulfurized to diphenylcarbodiimide; alkali cyanide added to the reaction mixture converts this to diphenylcarbodiimide hydrocyanide. With yellow ammonium sulfide the latter gives a thioamide, which condenses in warm concentrated sulfuric acid to 2-isatin anil [Ger. Pats. 113978–81 (1899), 115465 (1899), 116563]:



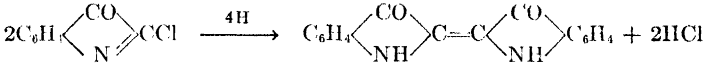
$$\begin{matrix}C_6H_5NH\\C_6H_5NH\end{matrix}\!\!>CS \xrightarrow[+HCN]{-H_2S} \begin{matrix}C_6H_5NH\\C_6H_5N\end{matrix}\!\!>C{\cdot}CN \longrightarrow \begin{matrix}C_6H_5NH\\C_6H_5N\end{matrix}\!\!>C{\cdot}CSNH_2 \longrightarrow C_6H_4\left\{\begin{matrix}CO\\NH\end{matrix}\right\}\!>C{:}NC_6H_5$$

The diphenylcarbodiimide hydrocyanide can also be converted directly to 2-isatin anil by warming with $AlCl_3$ (Ger. Pat. 277396, 1913).

2-Isatin anil is also obtained by the condensation of diphenylisonitrosoacetamidine, $\begin{matrix}C_6H_5NH\\C_6H_5N\end{matrix}\!\!>C{\cdot}CH{:}NOH$, from aniline, hydroxylamine and chloral, with sulfuric acid (*Sandmeyer,* Helv. **2,** 334).

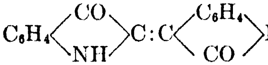
With H_2S in acid solution 2-isatin anil forms **2-thioisatin,** which very readily loses sulfur to give indigo, but with alkaline lead solution yields isatin (Ger. Pat. 131934, 1901). Ammonium sulfide reduces 2-isatin anil in the cold to indoxyl and in a warm reaction mixture to indigo (*Pummerer, Gottler,* Ber. **43,** 1379). When reduced with sodium hydrosulfite the isatin anils add two atoms of hydrogen, forming the colorless **leuco-isatin anils,** $C_8H_6NO{\cdot}NHC_6H_5$, which are oxidized to the isatin anils by the oxygen in the air (*Pummerer, Gottler,* Ber. **43,** 1376). **Isatin dianil,** $C_6H_4(C{:}NC_6H_5)_2NH$, m.p. 210°.

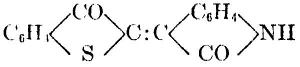
10. Warming isatin with PCl_5 in benzene solution produces **isatin-2-chloride, 2-chloro-3-pseudoindolone,** $C_6H_4\left\langle\begin{matrix}CO\\N\end{matrix}\right\rangle\!\!\!/\,CCl$, m.p. 180° (dec.), which dissolves in ether to a blue solution; it is converted by reduction with HI in glacial acetic acid or with zinc dust to *indigo*:



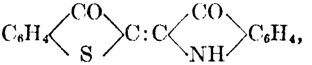
$$2C_6H_4\left\langle\begin{matrix}CO\\N\end{matrix}\right\rangle CCl \xrightarrow{4H} C_6H_4\left\langle\begin{matrix}CO\\NH\end{matrix}\right\rangle C{=}C\left\langle\begin{matrix}CO\\NH\end{matrix}\right\rangle C_6H_4 + 2HCl$$

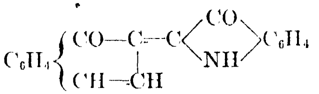
Substituted indigos, such as *dibromo-*, *dinitro-* and *dimethylindigo*, are prepared by this reaction from isatins substituted in the benzene nucleus.

11. With compounds containing an activated methylene group isatin condenses to dyestuffs which resemble indigo in structure and behavior, and which are therefore termed **indigoid dyes.** Isatin and indoxyl form *indirubin*,  $C_6H_4\left\langle\begin{matrix}CO\\NH\end{matrix}\right\rangle C{:}C\left\langle\begin{matrix}C_6H_4\\CO\end{matrix}\right\rangle NH$ (p. 70), and isatin and 3-thianaphthenol form the valuable *thioindigo scarlet R*:



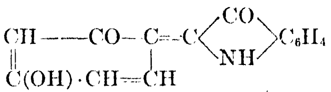
$$C_6H_4\left\langle\begin{matrix}CO\\S\end{matrix}\right\rangle C{:}C\left\langle\begin{matrix}C_6H_4\\CO\end{matrix}\right\rangle NH$$

(*Bezdzik*, *Friedländer*, Mo. 29, 376). While in isatin itself it is the carbonyl in the 3-position which reacts, in isatin derivatives, such as isatin 2-chloride, isatin 2-anil and O-methylisatin, the condensation takes place at the 2-carbon, with loss of HCl, $C_6H_5NH_2$, and CH_3OH and formation of the isomeric dyestuffs, *indigo* with indoxyl, and *Ciba violet A*,  $C_6H_4\left\langle\begin{matrix}CO\\S\end{matrix}\right\rangle C{:}C\left\langle\begin{matrix}CO\\NH\end{matrix}\right\rangle C_6H_4$, with 3-thianaphthenol (*Bezdzik*, *Friedländer*, Mo. 29, 377; *Felix*, *Friedländer*, Mo. **31**, 55). Isatin 2-chloride or isatin 2-anilide also reacts with those phenols which tend to form keto tautomers, such as 1- and 2-naphthol, anthrols, and resorcinol, producing blue to blue-violet indigoid vat dyes (*Bezdzik*, *Friedländer*, Mo. **29**, 375; **30**, 271, 871; *Friedländer*, *Schuloff*, Mo. **29**, 387):



$$C_6H_4\left\{\begin{matrix}CO{-}C{=}C\left\langle\begin{matrix}CO\\NH\end{matrix}\right\rangle C_6H_4\\ CH{-}CH\end{matrix}\right.$$

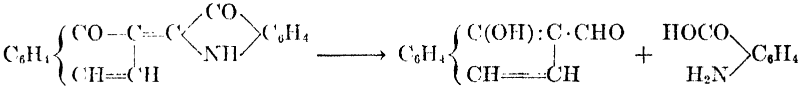
2-(1-Oxo-1,2-dihydro-2-naphthylidene)-pseudoindoxyl



$$\begin{matrix}CH{-}{-}CO{-}C{=}C\left\langle\begin{matrix}CO\\NH\end{matrix}\right\rangle C_6H_4\\ \| \qquad\qquad | \\ C(OH)\cdot CH{=}CH\end{matrix}$$

2-(4-Hydroxy-2-oxo-1-cyclohexadienylidene)-pseudoindoxyl

These dyestuffs are split more or less readily by alkali into anthranilic acid and the corresponding aldehyde:



$$C_6H_4\left\{\begin{matrix}CO{-}C{=}C\left\langle\begin{matrix}CO\\NH\end{matrix}\right\rangle C_6H_4\\ CH{=}CH\end{matrix}\right. \longrightarrow C_6H_4\left\{\begin{matrix}C(OH){:}C\cdot CHO\\ CH{=}CH\end{matrix}\right. + \begin{matrix}HOCO\\H_2N\end{matrix}\Big\rangle C_6H_4$$

Compare the analogous fission of indigo, p. 82.

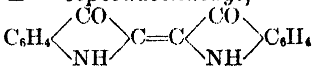
12. When isatin is treated with an ethereal solution of diazomethane, the principal product is 2,3-*quinolinediol*, formed by an enlargement of the pyrrole ring (*Heller*, Ber. **59**, 704; *Arndt*, *Eistert*, *Ender*, Ber. **62**, 49).

13. For condensation products of isatin and phenylhydroxylamine, see *Rupe*, *Stöcklin*, Helv. **7**, 557.

5-Nitroisatin, m.p. 254° (?) (*Calvery*, *Noller*, *Adams*, Am. **47**, 3058; *Rupe*, *Kersten*, Helv. **9**, 578). **6-Nitroisatin,** m.p. 244° (*Rupe*, *Kersten*, Helv. **9**, 578).

α-Naphthisatin, 1-*benz(g)indole*-2,3-*dione*, $C_{10}H_6(C_2O_2)NH$, m.p. 255°; **β-naphthisatin,** 3-*benz(e)indole*-1,2-*dione*, m.p. 248° (*Hinsberg*, Ber. **21**, 117; *Wichelhaus*, Ber. **36**, 1736; Ger. Pat. 152019, 1902).

Indigo (*indigotin*), $\Delta^{2,2'}$-*bipseudoindoxyl*,



$$C_6H_4\left\langle\begin{matrix}CO\\NH\end{matrix}\right\rangle C{=}C\left\langle\begin{matrix}CO\\NH\end{matrix}\right\rangle C_6H_4$$

is the principal constituent of commercial indigo obtained from the different types of *Indigofera* (*Indigofera tinctoria, anil, etc.;* China, India) and in small amount from woad (*Isatis tinctoria;* Europe) and dyer's collinsia (*Polygonum tinctorium*). For the detection of indigo in plants, see *Neger,* Flora **16** (1923), 323. *Indican,* the substance in these plants which forms indigo, is a glucoside of indoxyl: C_8H_6O-$N(C_6H_{11}O_5)$; for its constitution, see *Macbeth, Pryde,* J. **121,** 1660. When the various portions of the plant are covered with water and allowed to stand in the air, this glucoside is split by the action of an enzyme into glucose and indoxyl, and the latter oxidizes to indigo in the air. Boiling dilute acids effect the same change as the enzyme. For more recent communications concerning the cultivation and processing of indigo plants, see "Chemische Industrie" (1914–1918) and Färber-Zeitung **1920,** 92. Most of the commercial indigo is now obtained synthetically (see p. 79).

The indigotin content of commercial indigo varies from 20 to 90%; the other constituents, such as *indigo gluten, indigo brown, indoxyl brown, indigo red,* and inorganic substances, have not been thoroughly investigated (*Perkin, Bloxam,* J. **91,** 279). Natural indigo is purified by reducing it to indigo white (p. 83), and precipitating it from a solution of the latter by shaking with air (*Fritzsche,* J.pr. [1] **28,** 193; *Sommaruga,* Ann. **195,** 305). Synthetic indigo is much purer than natural indigo. The indigotin content is determined by titration with hydrosulfite or potassium permanganate.*

History (*cf.* Ber. **33,** Sonderheft p. LI).—Indigo was known and prized in ancient times by the Oriental nations (*Dioscorides, Plinius:* ἰνδιχον, indicum). In Europe up to the 18th century indigo was obtained from woad; this indigo was completely displaced by the East Indian indigo from Bengal, Java, and that from Central America. As the synthetic methods have improved, natural indigo has become less and less important in commerce.

The first important chemical attack upon the dyestuff molecule, by the oxidation of indigo to isatin with nitric acid, was carried out simultaneously by *Erdmann* and *Laurent* in 1841. In 1848 *Fritzsche* observed the formation of aniline when indigo was distilled with KOH. In 1865 *Baeyer* and *Knop* reduced isatin stepwise to 3-hydroxyoxindole, oxindole and indole; the latter was synthesized by *Baeyer* and *Emmerling* (Ber. 2, 679) in 1869 from *o*-nitrocinnamic acid. In 1870 *Engler* and *Emmerling* (Ber. **3,** 887; **28,** 309) reported the first synthesis of indigo by heating *o*-nitroacetophenone with Zn dust and lime, in 1874 *Nencki* obtained indigo from indole by oxidation with ozone. *Baeyer* and his students (1870–1878) reported the constitution of oxindole, its synthesis from *o*-nitrophenylacetic acid, and its conversion to isatin, as well as a number of methods of forming indigo from isatin. Isatin was prepared from *o*-aminobenzoylformic acid by *Claisen* and *Shadwell* in 1879. During 1880 to 1882 a series of new syntheses of indigo were discovered by *Baeyer,* providing more certain evidence of its constitution and easier methods for its production. The first patent on the preparation of indigo, from *o*-nitrophenylpropiolic acid, was granted on March 19, 1880; Ger. Pat. 11857; Frdl. **I,** 127. Of the many indigo syntheses developed since that time, that from phenylglycine-*o*-carboxylic acid (introduced technically in 1897 by Badische Anilin- und Sodafabrik), and that from phenylglycine, discovered in 1890 simultaneously by *Heumann* (Ber. **23,** 3043) and *Lederer* (J.pr. **42,** 383) and put into industrial use in 1901 by the *Höchster Farbwerke,* have proved practical.

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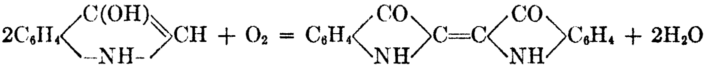
* For details, see the book: *Indigo rein,* Badische Anilin- und Sodafabrik, Ludwigshafen (1907), pp. 13–21; also *Jones, Spaans,* Ind.Eng.Chem. **8** (1917), 1001.

Synthesis of Indigo

Most methods for the preparation of indigo start from *isatin* or *indoxyl* or their derivatives; probably the formation of natural indigo is also accomplished by the oxidation of indoxyl (*cf.* p. 78).

1. Indoxyl is converted to indigo by oxidation (p. 69):

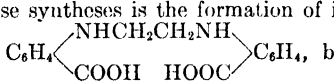


$$2C_6H_4\Big<\begin{matrix}C(OH)\\ -NH-\end{matrix}\Big>CH + O_2 = C_6H_4\Big<\begin{matrix}CO\\ NH\end{matrix}\Big>C{=}C\Big<\begin{matrix}CO\\ NH\end{matrix}\Big>C_6H_4 + 2H_2O$$

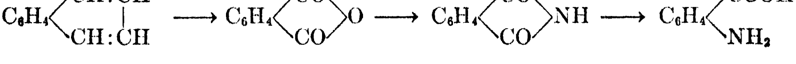
For the preparation of *indoxyl* or its derivatives, two methods are in technical use:

(*a*) The first of these methods is based on *Heumann's* discovery (1890) of the formation of indoxyl from N-*phenylglycine*, $C_6H_5NH\cdot CH_2COOH$, by alkali fusion. The addition of sodium amide lowers the temperature of fusion and thereby makes the reaction suitable for large-scale operation (Ger. Pat. 137955, 1901; Frdl. **VI**, 567).

Tolyl-, xylyl-, naphthyl- and phenylmethylglycine, used in place of phenylglycine, form derivatives of indigo; with fuming sulfuric acid these compounds give the corresponding indigosulfonic acids. Indoxyl is also produced by the fusion of N-(2-*hydroxyethyl*)-*aniline*, $C_6H_5NH\cdot CH_2CH_2OH$, (Ger. Pat. 171172, 1904), of N,N'-*diphenylethylenediamine*, $C_6H_5NHCH_2\cdot CH_2NHC_6H_5$ (Ger. Pat. 220172, 1908), of *phenylhydantoin*, of *α-bromoacetanilide*, $C_6H_5NHCO\cdot CH_2Br$, and of *diphenylpiperazinedione* with KOH (*Biedermann, Lepetit,* Ber. **23**, 3289; *Kuhara, Chikashigé,* Am.Chem.J. **24**, 167; **27**, 1; Ger. Pat. 149638, 1903). Similar to these syntheses is the formation of indigo from N,N'-ethylenedianthranilic acid, $C_6H_4\Big<\begin{matrix}NHCH_2CH_2NH\\ COOH\quad HOOC\end{matrix}\Big>C_6H_4$, by fusion with alkali (*Fränkel, Spiro,* Ber. **28**, 1685).

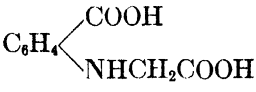


(*b*) Anthranilic acid is the starting material for the other technical method for the preparation of indoxyl and its derivatives. It is obtained from naphthalene, which is present in coal tar in abundance. The latter is oxidized to phthalic anhydride with mercury and sulfuric acid, and this is converted to phthalimide with NH_3. The imide is transformed by bromine and alkali to anthranilic acid:



$$C_6H_4\Big<\begin{matrix}CH{:}CH\\ |\\ CH{:}CH\end{matrix} \longrightarrow C_6H_4\Big<\begin{matrix}CO\\ CO\end{matrix}\Big>O \longrightarrow C_6H_4\Big<\begin{matrix}CO\\ CO\end{matrix}\Big>NH \longrightarrow C_6H_4\Big<\begin{matrix}COOH\\ NH_2\end{matrix}$$

Anthranilic acid is converted to N-*carboxymethylanthranilic acid*

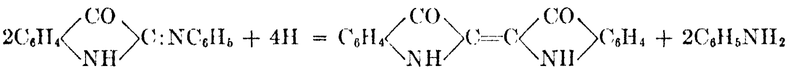


$$C_6H_4\Big<\begin{matrix}COOH\\ NHCH_2COOH\end{matrix}$$

by one of these methods: (*1*) heating with chloroacetic acid; (*2*) condensation with formaldehyde and HCN, followed by saponification; (*3*) fusion with polyhydroxy compounds, such as glycerol, mannitol, glucose, or cellulose, and caustic alkali (*Ostromisslensky, Pamfilow,* Ber. **43**, 2774). This glycine derivative is condensed by fusion with alkali in the absence of air or by heating with acetic anhydride to indoxyl derivatives (p. 69), which are converted to indigo by the reaction shown above.

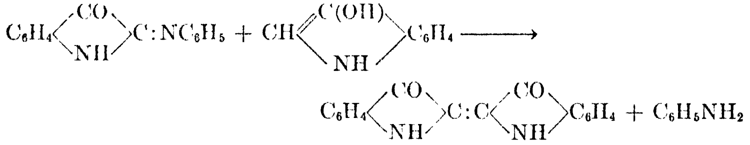
Compare the formation of indoxylcarboxylic acid ester from N-*carboxymethylanthranilic acid ester* and from *anilinomalonic acid ester*, and its conversion to indoxylic acid and indoxyl (p. 69).

* *2a.* Indigo is obtained from *isatin* in either of two ways: isatin 2-chloride is condensed with zinc dust (*cf.* p. 77), or isatin 2-anil is treated with ammonium sulfide (Ger. Pat. 119280, 1899):



$$2C_6H_4\left\langle\begin{matrix}CO\\NH\end{matrix}\right\rangle C{:}NC_6H_5 + 4H = C_6H_4\left\langle\begin{matrix}CO\\NH\end{matrix}\right\rangle C{=}C\left\langle\begin{matrix}CO\\NH\end{matrix}\right\rangle C_6H_4 + 2C_6H_5NH_2$$

2b. Isatin 2-chloride and isatin 2-anil condense with indoxyl when warmed in benzene or glacial acetic acid to form indigo by splitting off HCl or aniline (*cf.* p. 77):

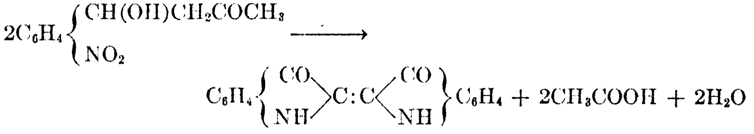


$$C_6H_4\left\langle\begin{matrix}CO\\NH\end{matrix}\right\rangle C{:}NC_6H_5 + CH\left\langle\begin{matrix}C(OH)\\NH\end{matrix}\right\rangle C_6H_4 \longrightarrow C_6H_4\left\langle\begin{matrix}CO\\NH\end{matrix}\right\rangle C{:}C\left\langle\begin{matrix}CO\\NH\end{matrix}\right\rangle C_6H_4 + C_6H_5NH_2$$

This method permits the preparation of unsymmetrical indigos. For the formation of isatin and isatin 2-anil, see pp. 74 and 76.

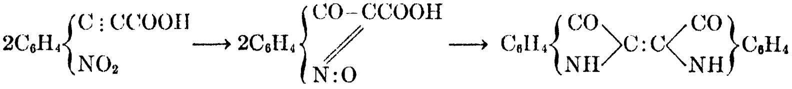
The next three syntheses of indigo were developed by *v. Baeyer* and his students, and are only of theoretical interest:

* *3.* *o*-Nitrobenzaldehyde condenses with acetone to 4-*o*-nitrophenyl-4-hydroxy-2-butanone (Vol. III, p. 406); with alkali this ketone is immediately converted to acetic acid, water and indigo:



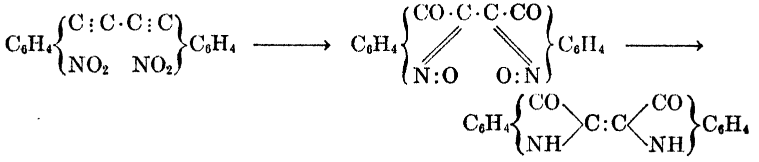
$$2C_6H_4\begin{cases}CH(OH)CH_2COCH_3\\NO_2\end{cases} \longrightarrow C_6H_4\left\{\begin{matrix}CO\\NH\end{matrix}\right\rangle C{:}C\left\langle\begin{matrix}CO\\NH\end{matrix}\right\} C_6H_4 + 2CH_3COOH + 2H_2O$$

* *4.* *o*-Nitrophenylpropiolic acid (Vol. III, p. 480), after rearrangement to isatogen-2-carboxylic acid, is reduced by alkaline reducing agents, with simultaneous decarboxylation, to indigo:



$$2C_6H_4\begin{cases}C{:}CCOOH\\NO_2\end{cases} \longrightarrow 2C_6H_4\begin{cases}CO{-}CCOOH\\ \quad /\!\!/\\N{:}O\end{cases} \longrightarrow C_6H_4\left\{\begin{matrix}CO\\NH\end{matrix}\right\rangle C{:}C\left\langle\begin{matrix}CO\\NH\end{matrix}\right\} C_6H_4$$

* *5.* *o*-Nitrophenylpropiolic acid can also be converted to indigo in this way: it is decarboxylated to *o*-nitrophenylacetylene, the copper derivative of which is condensed by potassium ferricyanide to *di(o-nitrophenyl)biacetylene;* the latter gives diisatogen with alkali, and this is reduced to indigo:



$$C_6H_4\left\{\begin{matrix}C{:}C{\cdot}C{:}C\\NO_2\quad NO_2\end{matrix}\right\} C_6H_4 \longrightarrow C_6H_4\left\{\begin{matrix}CO{\cdot}C{\cdot}C{\cdot}CO\\ /\!\!/ \qquad \backslash\!\!\backslash\\N{:}O\quad O{:}N\end{matrix}\right\} C_6H_4 \longrightarrow C_6H_4\left\{\begin{matrix}CO\\NH\end{matrix}\right\rangle C{:}C\left\langle\begin{matrix}CO\\NH\end{matrix}\right\} C_6H_4$$

6. When *o*-nitroacetophenone, $C_6H_4(NO_2)COCH_3$, is carefully heated with zinc

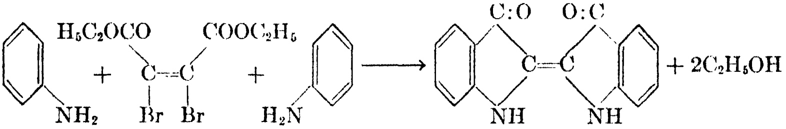
dust, a small amount of indigo sublimes. 2-*Nitrochalcone*, $C_6H_4\left\langle\begin{matrix}COCH:CHC_6H_5\\NO_2\end{matrix}\right.$, reacts with itself in sunlight to give indigo and benzoic acid (*Engler, Dorant*, Ber. **28**, 2497).

7. When warmed with caustic alkali and reducing agents, *o-nitrobenzoylacetic acid*, $C_6H_4\left\langle\begin{matrix}CO\cdot CH_2COOH\\NO_2\end{matrix}\right.$, or its ester condenses to indigo (Ger. Pat. 201108, 1907).

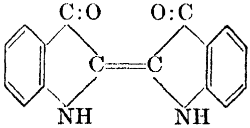
8. N-*Hydroxyindolecarboxylic acid*, from *o*-nitrobenzylmalonic ester or *o*-nitrophenylpyruvic acid is converted to indigo by treatment with concentrated sulfuric acid and subsequent oxidation with air:

$$2C_6H_4\left\{\begin{matrix}CH_2COCOOH\\NO_2\end{matrix}\right. \longrightarrow 2C_6H_4\left\{\begin{matrix}CH=\\N(OH)\end{matrix}\right\rangle CCOOH \longrightarrow C_6H_4\left\{\begin{matrix}CO\\NH\end{matrix}\right\rangle C:C\left\langle\begin{matrix}CO\\NH\end{matrix}\right\}C_6H_4$$

9. A synthesis of purely theoretical interest, which indicates clearly the structure of indigo, is the reaction of *dibromomaleic acid ester* with *aniline*. The first intermediate product is *dianilinomaleic acid ester*, which condenses to indigo when heated with sodium amide (*Mohr*, Ber. **38**, 2600):



Constitution of Indigo.—The formula of indigo, proposed by *A. v. Baeyer* (Ber. **16**, 2188) in 1883 shows it as a derivative:



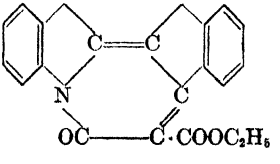
of the yellow *cis-dibenzoylethylene*,

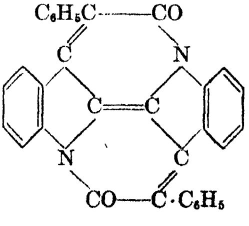
$$\begin{matrix}C_6H_5\cdot CO & & CO\cdot C_6H_5.\\ & \diagdown\quad\diagup & \\ & CH{=}CH & \end{matrix}$$

According to *Friedländer* (Mo. **29**, 359), the deep color of indigo is explained by the presence of the chromophoric grouping: CO·C=C·CO.

However, more recent investigations provide evidence that indigo is derived from *trans-dibenzoylethylene*, which is colorless. The reaction products of indigo and *malonic ester* (formula I; *Posner, Pyl*, Ber. **56**, 31) and of indigo and *phenylacetic acid ester* (formula II; Lackrot-Ciba B; *Posner, Kemper*, Ber. **57**, 1313):

I

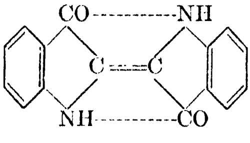


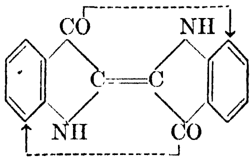


II

can be explained only by the existence of a *trans* form for indigo. In indigo the CO- and the NH-groups do not possess normal reactivity; the *trans* form of indigo might account for this by the presence of residual valences between neighboring CO- and NH-groups (*Scholl-Madelung*, formula III; Ber. **57,** 237), or between the CO-groups and the benzene nuclei (*Posner*, Ber. **59,** 1873, formula IV), which mask the activity of the groups:

III





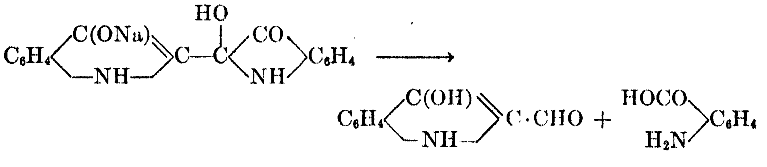
IV

These formulas also explain the failure to obtain space-isomers of indigo dyes. Formula IV shows indigo as an intramolecular quinhydrone, which would account for its intense color (*Posner*, Ber. **59,** 1843).

Properties.—Indigo is a dark blue powder which acquires a copper-red, metallic sheen on grinding. It has a very high melting point, and on subliming forms copper-red metallic prisms. It is insoluble in water, alcohol, ether, alkalies and dilute acids; it is soluble in many high-boiling solvents, such as aniline, phenol, nitrobenzene, tetralin, and quinoline, as well as in chloroform. It crystallizes from chloroform in especially fine crystals, and from hot oil of turpentine and from molten phthalic anhydride in beautiful blue crystals. It is converted by heat to a dark red vapor, with carbonization at ordinary pressure, but with no decomposition at 30–40 mm.

For the absorption spectra of indigo and its derivatives, see *Friedländer, Kunz,* Ber. **55,** 1598; *Hantzsch, Bucerius,* Ber. **59,** 814; *Formanek,* Z.angew.Chem. **1928,** 1133.*

Indigo combines with both acids and alkalis. Addition of ether to a solution of indigo in glacial acetic acid-sulfuric acid precipitates the crystalline sulfate, $C_{16}H_{10}N_2O_2 \cdot SO_4H_2$ (*Binz, Kufferath,* Ann. **325,** 196). In the presence of water the indigo salts are immediately hydrolyzed; this property is used technically to obtain very finely divided indigo (Ger. Pat. 272233, 1911, Frdl. **XI,** 318; Ger. Pat. 275290, 1912, Frdl. **XI,** 320). When indigo is treated with a concentrated aqueous solution of sodium hydroxide or sodium alcoholate, an addition product, $C_{16}H_{10}N_2O_2 \cdot NaOH$ (constitution: *Friedländer,* Ber. **41,** 1035) is obtained in the form of a dark green powder, which dissociates in water and is decomposed by energetic treatment with alkali into indoxyl-2-carboxaldehyde and anthranilic acid (discovery of anthranilic acid, 1848) (*Friedländer, Schwenk,* Ber. **43,** 1971):



$$C_6H_4\left\langle\begin{matrix}C(ONa)\\NH\end{matrix}\right\rangle C{-}\overset{HO}{C}\left\langle\begin{matrix}CO\\NH\end{matrix}\right\rangle C_6H_4 \longrightarrow C_6H_4\left\langle\begin{matrix}C(OH)\\NH\end{matrix}\right\rangle C{\cdot}CHO + \begin{matrix}HOCO\\H_2N\end{matrix}\!\!>C_6H_4$$

When indigo is treated with the usual reagents for ketones, usually only one of the two carbonyl groups reacts. With alkaline hydroxylamine solution indigo forms a monoxime, $C_{16}H_{10}N_2O(NOH)$, brown-violet needles, m.p. 205° (dec.) (*Thiele, Pickard,* Ber. **31**, 1252). However, zinc chloride-ammonium chloride at a high temperature yields both a *monoimine* and *indigodiimine*, dec. above 200° (*Madelung,* Ber. **46**, 2259); the latter reacts readily with hydroxylamine, hydrazine, and phenylhydrazine to give the *dioxime, azine,* m.p. over 300°, and *bisphenylhydrazone,* m.p. 220°. *Dianil: Grandmougin, Dessoulavy,* Ber. **42**, 3636.

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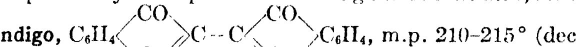
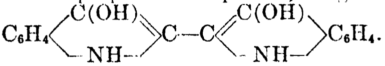
* *Cf. Formanek-Knop,* Untersuchung und Nachweis organischer Farbstoffe auf spektroskopischem Wege, Teil III. Springer, Berlin, 1929.

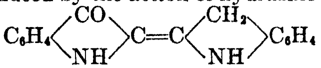
Oxidation with nitric acid, chromic acid or potassium permanganate solution attacks the C:C-bridge of indigo, producing isatin.

Oxidation with PbO_2, Ag_2O, or $KMnO_4$ in indifferent solvents in the absence of water, and preferably in the presence of some glacial acetic acid, converts indigo to **dehydroindigo,**  $C_6H_4\langle{}^{CO}_{N}\rangle C-C\langle{}^{CO}_{N}\rangle C_6H_4$, m.p. 210–215° (dec.), dark yellow plates. It is much more soluble in organic solvents than indigo is. It has a strongly oxidizing action, behaves like a quinone, and is readily reduced to indigo. It forms bright yellow salts with two mols of acid. With sodium bisulfite it gives a crystalline addition product, $C_{16}H_8N_2O_2\cdot 2NaHSO_3 + 2H_2O$, bright canary yellow, soluble in water; this can be halogenated, and subsequently decomposed with boiling dilute acids, to give halogenated indigotins (*Kalb,* Ber. **42**, 3642, 3653). Aqueous mineral acids split dehydroindigo into 3-*hydroxyoxindole* and *isatin* (*Kalb,* Ber. **44**, 1455).

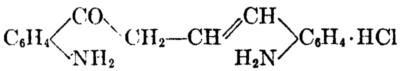
Neutral permanganate solution yields another oxidation product, yellow crystals, m.p. 261° (Ger. Pat. 281050, 1913; constitution: *Friedländer, Roschdestwensky,* Ber. **48**, 1841).

When indigo in alcoholic suspension is treated with nitrous gases, phenylglyoxylic acid ethyl ester is obtained (*Posner, Aschermann,* Ber. **53**, 1925).

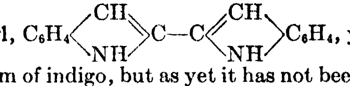
Reduction Products of Indigo.—**Indigo white,** $C_{16}H_{12}N_2O_2$, is formed by the reduction (vatting) of indigo with zinc dust and alkali, hydrosulfite, ferrous hydroxide and alkali or H_2S in the presence of pyridine [*Binz, Prange,* Z. angew. Chem. **40** (1927), 1474] and by biochemical reduction (steeping vat). In the absence of air it can be precipitated from its alkaline solution with hydrochloric acid in the form of white crystals, which dissolve in alcohol, ether and alkalis to yellow solutions. In the air it oxidizes to indigo, a property which is the basis of vat dyeing. Since it is derived from indigo by the addition of two H-atoms, and has the properties of a phenol, indigo white is assigned the formula of a *biindoxyl,*  $C_6H_4\langle{}^{C(OH)}_{NH}\rangle C-C\langle{}^{C(OH)}_{NH}\rangle C_6H_4$. For acyl and alkyl derivatives of indigo white, see *Madelung, Wilhelmi,* Ber. **57**, 241.

Desoxyindigo, green-yellow, m.p. 317°, is produced by the action of hydrazine hydrate on indigo in alcoholic suspension:  $C_6H_4\langle{}^{CO}_{NH}\rangle C{=}C\langle{}^{CH_2}_{NH}\rangle C_6H_4$ (*Borsche, Meyer,* Ber. **54**, 2854).

Indigo and indigo white are converted by tin and hydrochloric acid to the hydrochloride of *o,o'-diaminostyrylacetophenone* (*Madelung,* Ber. **57**, 222):

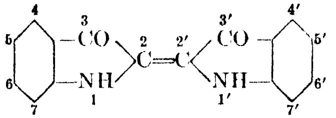


$$C_6H_4\langle{}^{CO}_{NH_2}\quad CH_2-CH{=}{}^{CH}_{H_2N}\rangle C_6H_4\cdot HCl$$

2,2'-Biindolyl,  $C_6H_4\langle{}^{CH}_{NH}\rangle C-C\langle{}^{CH}_{NH}\rangle C_6H_4$, yellowish crystals, m.p. 300°, is a reduced form of indigo, but as yet it has not been obtained from indigo. It is synthesized from oxalyl-*o*-toluidine, and can be oxidized to indigo (*Madelung,* Ann. **405**, 58, 61).

Derivatives and Substitution Products of Indigo

Indigo, or indigotin, is numbered in this way:



(*a*) *Substituents in the NH-group.*—Complex compounds of indigo with various metals (Cu, Zn, Ni) are formed by the displacement of the hydrogen atoms in the NH-groups of two molecules of indigo, when it is boiled with metals, metal oxides, metal acetates, or iron carbonyl in anhydrous high-boiling solvents (*Kuhn, Machemer*, Ber. **61**, 118).

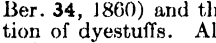
N,N′-DIALKYLINDIGOTINS, which are blue to blue-green dyes, are usually obtained from the corresponding phenylglycines: **1,1′-dimethylindigotin**, green-blue (*Ettinger, Friedländer*, Ber. **45**, 2074); **1,1′-diethylindigotin** (*Baeyer*, Ber. **16**, 2202); **1,1′-diphenylindigotin** (*Friedländer, Kunz*, Ber. **55**, 1597).

1,1′-DIACYLINDIGOTINS: **1,1′-Dibenzoylindigotin**, m.p. 258°, dark violet, prepared by boiling indigo with benzoyl chloride in pyridine (*Posner*, Ber. **59**, 1804). The technically important product formed by boiling benzoyl chloride and indigo in nitrobenzene in the presence of Cu-powder, which is called indigo yellow, is a derivative of anthraquinone (constitution: *Posner, Hofmeister*, Ber. **59**, 1827). The simpler condensation of indigo and phenylacetyl chloride forms *Lackrot Ciba B* (formula on p. 81).

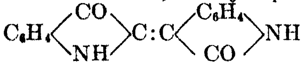
(*b*) *Substituents in the benzene nuclei.*—**Sulfonic acids**: Up to four sulfonic acid groups (first in the 5,5′- then in the 7,7′-positions) can be introduced into the indigo molecule by the action of sulfuric acid. Since the sulfonic acids of indigo are soluble in water, **indigotin-5,5′-disulfonic acid** (*Vorländer, Schubart*, Ber. **34**, 1860) and the **5,5′,7,7′-tetrasulfonic acid** are useful for the direct fixation of dyestuffs. Alkali salts of indigotindisulfonic acid are sold in paste form under the name *indigo carmine*.

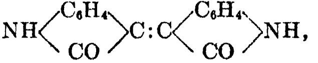
(*c*) *Halogenated indigotins.*—The halogenated indigotins are of considerable technical importance, especially those substituted in the 5- and 7-positions, which dye bright greenish shades of excellent fastness. Halogen in the 6-position gives violet-red dyes. **5,5′,7,7′-Tetrachloroindigotin**, *brilliant indigo*; **5,5′,7,7′-tetrabromoindigotin**, *Ciba blue*. They are obtained by direct halogenation of indigo in the absence of water, preferably in warm nitrobenzene solution (Ger. Pat. 193438, 1907) or in cold concentrated sulfuric acid or chlorosulfonic acid, or by the action of halogen on the sodium bisulfite compound of dehydroindigo (p. 83) (*Grandmougin*, Ber. **42**, 4408; **43**, 937). **5,5′,7,7′-Tetraiodoindigotin** (*Kalb, Berrer*, Ber. **57**, 2105); **4,4′-dichloroindigotin**, from 2-nitro-6-chlorobenzaldehyde (*Gindraux*, Helv. **12**, 931). **6,6-Dibromoindigotin**, dark violet crystals with a coppery luster, has been found to be identical with the purple of antiquity, gathered from the secretion of the purple snail (*Murex brandaris*). It dyes the fiber dark reddish violet shades (*Friedländer*, Ber. **42**, 765). For a new synthesis of this dyestuff from 6-bromoindole-3-carboxylic acid with ozone, see *Majima, Kotake*, Ber. **63**, 2237.

7,7′-Dimethylindigotin (*Grandmougin, Dessoulavy*, Ber. **42**, 3641).

Indigotindicarboxylic acid is formed from *o*-nitrophthalaldehydic acid,  $C_6H_3(COOH)\Big\langle\begin{smallmatrix}CHO\\ NO_2\end{smallmatrix}$, as indigo is formed from *o*-nitrobenzaldehyde.

These compounds are isomeric with indigo:

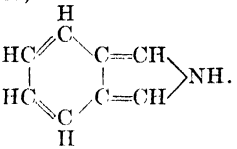
1. **Indirubin**, *indigo purpurin, indigo red*, $\Delta^{2,3'}$-biindoline-3,2′-dione,  $C_6H_4\Big\langle\begin{smallmatrix}CO\\ NH\end{smallmatrix}\Big\rangle C:C\Big\langle\begin{smallmatrix}C_6H_4\\ CO\end{smallmatrix}\Big\rangle NH$, reddish needles, subliming undecomposed over 340°, is the indogenide of oxindole; it occurs with indigo in plants and is synthesized by condensation of isatin with indoxyl (p. 84), or of isatin 2-chloride or 2-anil with oxindole. For the absorption spectra of indirubin and its derivatives, see *Formanek*, Z.angew Chem. **41** (1928), 1133.

2. **Isoindigotin**, $\Delta^{3,3'}$-*bioxindole*,  $NH\Big\langle\begin{smallmatrix}C_6H_4\\ CO\end{smallmatrix}\Big\rangle C:C\Big\langle\begin{smallmatrix}C_6H_4\\ CO\end{smallmatrix}\Big\rangle NH$, garnet-red needles, is obtained by condensation of oxindole with isatin (p. 73) (*Wahl, Bayard*, C.r. **148**, 716).

β-Naphthindole, *3-benz(e)indole*, $C_{10}H_6\left\{\begin{array}{l}[\alpha]CH\diagdown\\ [\beta]NH\diagup\end{array}\right.\!\!CH$, is obtained from its sulfonic acid (see below) (*Hinsberg, Simcoff*, Ber. **31**, 251).

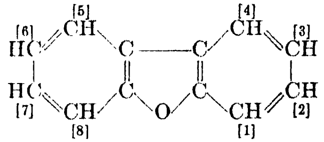
Bis-2,2′-naphthindole-(2,1,2′,1′)-indigo, *Δ$^{2,2'}$-bi-(1-benz(g)indol-3(2)-one)* and **bis-2,2′-naphthindole(1,2,1′,2′)-indigo**, *Δ$^{2,2'}$-bi-(3-benz(e)indol-3(2)-one)*, are obtained from the naphthylglycines by fusion with alkali and subsequent oxidation (*Wichelhaus*, Ber. **26**, 2547), and from the benzindoxylic acid esters, prepared from naphthylaminomalonic acid esters (*Wichelhaus*, Ber. **32**, 1236). *Bis-2,2′-naphthindole-(2,3,2′,3′)-indigo, Δ$^{2,2'}$-bi-(benz(f)indol-3(2)-one)* (***Fierz**, Tabler*, Helv. **5**, 557); *perinaphthindigo* (*Fierz, Sallmann*, Helv. **5**, 560); ***naphth**isoindigotin* (*Wahl, Lobeck*, C.r. **188**, 1683).

8. **ISOINDOLE**, 2-benzo[*c*]pyrrole,

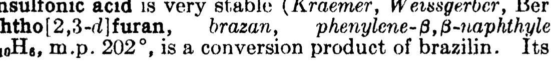


N-Acetyldihydroisoindole, m.p. 76°, hydrochloride, m.p. 256°, has been obtained by electrolytic reduction of phthalimide (*Späth, Breusch*, Mo. **50**, 349).

9. **DIBENZOFURAN**, biphenylene oxide,



m.p. 81°, b.p. 288°, occurs in small quantities in *stubb-fat* and in the fluorene fraction of coal tar, in which it can be detected by conversion to *o,o′*-biphenol in fused alkali (*Kraemer, Weissgerber*, Ber. **34**, 1662). Dibenzofuran is synthesized: (*1*) by distillation of phenyl phosphate (Vol. III, p. 195) with lime; (*2*) from phenol with lead oxide; (*3*) from phenyl ether by passage through an incandescent tube; (*4*) from *o,o′*-biphenol, $HO[2]C_6H_4\cdot C_6H_4[2]OH$, by melting with zinc chloride (*ibid.*, p. 1663); (*5*) from the diazo compound of *o*-phenoxyaniline with sulfuric acid, as 9-fluorenone is formed from *o*-aminobenzophenone; (*6*) most advantageously, from the tetrazo compound of 2,2′-diaminobiphenyl with dilute acids (*Täuber, Halberstadt*, Ber. **25**, 2746):

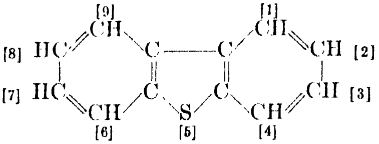


$$C_6H_4\underset{\diagdown NH_2\qquad H_2N\diagup}{\rule{6em}{0.4pt}}C_6H_4 \xrightarrow{N_2O_3} C_6H_4\underset{\diagdown O\diagup}{\rule{3em}{0.4pt}}C_6H_4$$

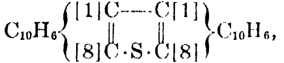
When fused with caustic alkali, dibenzofuran forms *o,o′*-biphenol (see above), when heated with $AlCl_3$, phenol (*Kraemer, Weissgerber*, Ber. **34**, 1664). With bromine, **dibromodibenzofuran**, m.p. 185°, is produced, and with fuming nitric acid, **dinitrodibenzofuran**, m.p. 200°. **Diaminodibenzofuran**, m.p. 188°, gives *substantive azo dyes*. **Dibenzofuran-3-carboxylic acid**, m.p. 246° (*Mayer, Krieger*, Ber. **55**, 1659). **Acetyldibenzofuran**, m.p. 81° (see *Galewsky*, Ann. **264**, 190). **Dibenzofuransulfonic acid** is very stable (*Kraemer, Weissgerber*, Ber. **34**, 1666). **Benzo**[*b*]**naphtho**[2,3-*d*]**furan**, *brazan, phenylene-β,β-naphthylene oxide*, $C_6H_4\underset{\diagdown O\diagup}{\rule{2em}{0.4pt}}C_{10}H_6$, m.p. 202°, is a conversion product of brazilin. Its derivatives are obtained by condensation of 2,3-dichloro-1,4-naphthoquinone with resorcinol and orcinol (*v. Kostanecki, Lampe*, Ber. **41**, 2373).

Dibenzofuran is reduced by sodium and alcohol to **tetrahydrodibenzofuran**, $C_6H_4\underset{\diagdown O\diagup}{\rule{2em}{0.4pt}}C_6H_8$, b.p. 269°. **Hexahydrodibenzofuran** is best obtained by catalytic hydrogenation (Ni, H_2 under pressure at 230°) of *o,o′*-biphenol (*v. Braun*, Ber. **55**, 3761). Under the same conditions, **dinaphtho**[2,1,1′,2′]**furan**, *β-dinaphthalene oxide*, $\underbrace{C_{10}H_6[\beta]—[\beta]C_{10}H_6}_{O}$, forms a tetrahydro derivative, but **dinaphtho**[1,2,2′,1′]**furan**, *α-dinaphthalene oxide*, $\underbrace{C_{10}H_6[\alpha]—[\alpha]C_{10}H_6}_{O}$, gives an octahydro derivative.

10. DIBENZOTHIOPHENE, diphenylene sulfide,

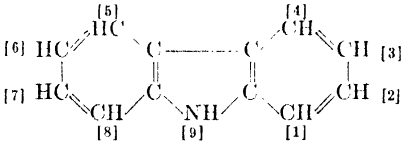


m.p. 97°, b.p. 333°, is formed on distillation of phenyl disulfide, $(C_6H_5)_2S_2$, and phenyl sulfide, $(C_6H_5)_2S$, through glowing tubes; a better method of preparation is the treatment of diphenyl sulfoxide, $(C_6H_5\cdot SO\cdot C_6H_5)$, with sodium amide in boiling toluene (*Schönberg*, Ber. **56**, 2275). It occurs in small amounts in coal tar (*Kraemer*, *Weissgerber*, Ber. **34**, 1665). In contrast to thiophene, it is oxidized by chromic acid to **diphenylene sulfone**, $(C_6H_4)_2SO_2$, m.p. 230°. **Diacenaphtho**[1,2-*b*, 1′,2′-*d*]**thiophene**,

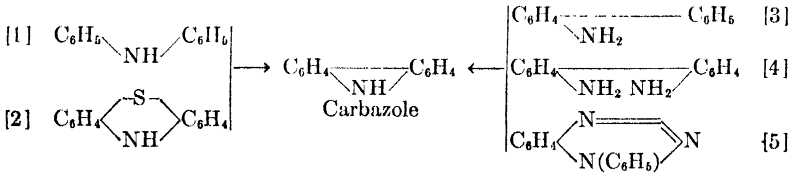


$C_{10}H_6\left\{\begin{matrix}[1]C\text{---}C[1]\\ \| \qquad \| \\ [8]C\cdot S\cdot C[8]\end{matrix}\right\}C_{10}H_6$, is formed by the condensation of acenaphthene and sulfur (*Rehländer*, Ber. **36**, 1583).

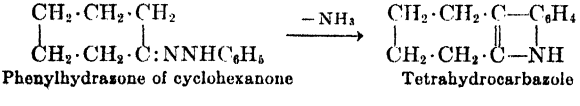
11. CARBAZOLE, 9-dibenzo[*b*,*d*]pyrrole, diphenylenimide,



m.p. 238°, b.p. 351°, is present in crude anthracene, from which it can be separated as the potassium salt by fusion with KOH. It is prepared (*1*) from diphenylamine by passage through an incandescent tube, or in the presence of a platinum catalyst at 300° (*Zelinsky*, *Titz*, *Gaverdowskaja*, Ber. **59**, 2590); (*2*) from phenothiazine by heating with copper powder; (*3*) from 2-aminobiphenyl by distillation over lime (*Blank*, Ber. **24**, 306); (*4*) from 2,2′-diaminobiphenyl by heating with acids (*Bamberger*, *Kitschelt*, Ber. **25**, 133); (*5*) from 2-aminodiphenylamine, through the diazo compound; the 1-phenyl-1,2,3-benzotriazole first formed splits into carbazole and nitrogen when heated to a high temperature (*Graebe*, *Ullmann*, Ann. **291**, 16; *Ullmann*, Ber. **31**, 1697):



(*6*) Carbazole derivatives are formed, similarly to the indoles (*cf.* method *d*, p. 63), from arylhydrazones of cyclohexanones (*Borsche*, Ann. **359**, 49); also, phenols which tend to tautomerize to the keto form, such as 2-naphthol and 9-hydroxyphenanthrene, yield carbazoles when heated with arylhydrazines and HCl:

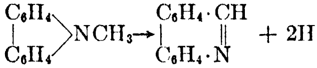


By similar reactions tetrahydrocarbazolecarboxylic acid is obtained from the phenylhydrazone of cyclohexanonecarboxylic acid, benzocarbazole and dibenzocarbazole are obtained from 2-naphthol with phenylhydrazine and with 1- and 2-naphthylhydrazine, and naphthobenzocarbazole is obtained from 9-hydroxyphenanthrene and naphthylhydrazine.

Properties.—Carbazole gives the *pine-shaving reaction* (p. 29) and the blue color reaction with isatin or aliphatic aldehydes and concentrated H_2SO_4 [*Dische*, Biochem.Z. **189** (1927), 77], like pyrrole and most indole compounds. It also produces a characteristic color when treated with concentrated sulfuric acid alone or with the addition of nitric acid (*Blom*, Helv. **4**, 625).

Carbazole condenses readily with nitrosophenols, forming dyestuffs similar to indophenol, which are converted by subsequent treatment with alkali polysulfides to valuable blue sulfur dyes (hydron blue dyes) (Ger. Pat. 218371, 1908, Frdl. **X**, 301).

Like pyrrole, carbazole is a very weak base, and forms a stable salt only with picric acid: picrate, m.p. 182°. Nitrous acid converts it to **9(N)-nitrosocarbazole,** $(C_6H_4)_2N\cdot NO$, m.p. 84°, which is rearranged by mineral acids to 3-nitrosocarbazole, $[C_{12}H_7(NO)]NH$; the latter can be reduced to 3-aminocarbazole. When heated with potassium hydroxide, carbazole forms a potassium compound, $(C_6H_4)_2NK$, which gives with alkyl iodides **9-methylcarbazole,** $(C_6H_4)_2N\cdot CH_3$, m.p. 87°, and 9-ethylcarbazole, m.p. 68°. When 9-methylcarbazole is passed through an incandescent tube, it is converted to *phenanthridine* (*Pictet*, Ber. **38**, 1950):



$$\left.\begin{matrix}C_6H_4\\|\\C_6H_4\end{matrix}\right\rangle NCH_3\rightarrow\begin{matrix}C_6H_4\cdot CH\\|\qquad\|\\C_6H_4\cdot N\end{matrix}+2H$$

Compare the analogous conversion of pyrrole to pyridine (p. 30) and of indole to quinoline (p. 62). **9-Acetylcarbazole,** m.p. 76°; **9-benzoylcarbazole,** m.p. 98°; for homologues, see *Bischoff*, Ber. **31**, 2847. With CH_3MgI carbazole reacts like pyrrole and indole (p. 65), producing methane and carbazolemagnesium iodide, $(C_6H_4)_2N\cdot MgI$. HNO_3 or, better, ethyl nitrate and conc. H_2SO_4 (*Raudnitz*, Ber. **60**, 738) yield nitrocarbazoles. **1-Nitrocarbazole,** m.p. 187° (*Lindemann*, Ber. **57**, 555). **3-Nitrocarbazole,** m.p. 214° (*loc. cit.*), is obtained from carbazole with N_2O_3, the N-nitroso compound being an intermediate in the reaction; it gives **3-aminocarbazole** on reduction. Because of their sensitivity to light, the diazo compounds of the latter are used in the production of photographic copies (*Ruff*, *Stein*, Ber. **34**, 1668). **1,3,6,8-Tetranitrocarbazole,** m.p. 289°, from carbazole with ethyl nitrate and concentrated sulfuric acid (*Raudnitz*, Ber. **60**, 738). **3,6-Diaminocarbazole,** m.p. over 290°, from the corresponding dinitrocarbazole. Fusion of carbazole with oxalic acid produces **tricarbazolemethanol,** or **carbazole blue** (for discussion of its constitution, see *Copisarov*, J. **117**, 1542).

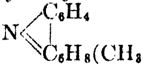
2-Methylcarbazole, m.p. 259°, and **3-methylcarbazole,** m.p. 203°, as well as many other alkylcarbazoles, are prepared from the corresponding tetrahydrocarbazoles, synthesized according to method *6* (p. 86), by distillation over gently heated lead oxide (*Borsche*, Ann. **359**, 74). **Dimethylcarbazole,** ditolyleneimine, $(CH_3\cdot C_6H_3)_2NH$, m.p. 364°, is formed pyrogenically from *o*-toluidine (*Seyberth*, Ber. **29**, 2594).

HALOGEN DERIVATIVES: 3-Chlorocarbazole, m.p. 192°; **3,6-dichlorocarbazole,** m.p. 202°.

CARBOXYLIC ACIDS: 9-Carbazolecarboxylic acid; 9-carbazoleacetic acid, m.p. 215° (ethyl ester, m.p. 97°) (Ger. Pat. 255304, 1911).

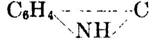
Oxidation of carbazole with Ag_2O in benzene produces **dibiphenylenehydrazine,** m.p. 296° (*Branch*, *Smith*, Am. **42**, 2405).

HYDROCARBAZOLES: 1,4-Dihydrocarbazole, m.p. 229°, by reduction of carbazole with sodium and amyl alcohol (*Schmidt*, *Schall*, Ber. **40**, 3225). **Tetrahydrocarbazole,** $NH\left\langle\begin{matrix}C_6H_4\\|\\C_6H_8\end{matrix}\right.$, m.p. 119°, is obtained by reduction of carbazole or from the phenylhydrazone of cyclohexanone (see method *6*, p. 86); it behaves like an alkylated indole. When treated with chloroform and sodium alcoholate, it is transformed to an acridine derivative, just as indoles are converted to quinoline derivatives. Like alkylindoles, on fusion with alkali it gives an indolecarboxylic acid (see p. 67 and *Zanetti*, Ber. **26**, 2006). The phenylhydrazone of 2-methyl-1-cyclohexanone is condensed by alcoholic zinc chloride to a carbazolenine,



$N\begin{smallmatrix}\diagup C_6H_4\\ |\\ \diagdown C_6H_8(CH_3)\end{smallmatrix}$

, analogous to the indolenines (p. 63). **Tetrahydrocarbazolecarboxylic acid,** m.p. 230°, is formed from the phenylhydrazone of cyclohexanonecarboxylic acid (*Baeyer, Tutein,* Ber. 22, 2185). **Hexahydrocarbazole,** *carbazoline,*



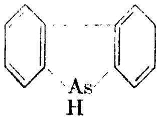
$C_6H_4\underset{NH}{\diagdown\!\!-\!\!-\!\!-\!\!\diagup}C_6H_{10}$

, *cis*-form (?), m.p. 99°, b.p. 267°, *trans*-form, m.p. 127° (*Gurney, Perkin, Plant,* J. **1927**, 2676), is obtained by heating carbazole or its less hydrogenated derivatives with phosphorus and hydriodic acid. Although carbazole itself is catalytically hydrogenated with difficulty, the N-alkylcarbazoles take up hydrogen immediately. *Tetrahydro-, hexahydro-, octahydro-* and *decahydro-9-alkylcarbazoles* are so prepared (*v. Braun, Ritter,* Ber. **55**, 3792). Like the hydrogenated pyrroles and indoles (p. 71) the hydrogenated carbazoles are strong bases (*Graebe, Glaser,* Ann. **163**, 352).

In preparation and properties the higher ring systems, containing naphthalene, anthracene, and phenanthrene rings, such as 1,2-benzocarbazole, 2,3-benzocarbazole, 3,4-benzocarbazole, and 1,2,3,4-dibenzocarbazole, are much like carbazole.

* * * * * *

Derivatives of **dibenzarsenole,** the arsenic analogue of carbazole:

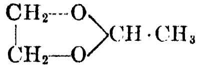


are known (*Aeschlimann, Lees, McClelland, Nicklin,* J. **127**, 66).

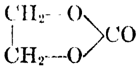
FIVE-MEMBERED RINGS WITH SEVERAL HETERO ATOMS

Five-membered rings containing two oxygen or sulfur atoms, not adjacent, occur in these compounds: the acetals and mercaptals of ethylene glycol, such as *ethylene ethylidene ether* (*2-methyl-1,3-dioxolane*) (I) and *ethylene ethylidene disulfide* (*2-methyl-1,3-dithiolane*) (II), the *ethylene ester of hydroxyformic acid, 1,3-dioxolan-2-one* (III), and its sulfur analogue, *1,3-dithiolane-2-thione* (IV), and the ethylidene esters of α-hydroxy acids, such as the *ethylidene ester of lactic acid* (*2,5-dimethyl-1,3-dioxolan-4-one*) (V) and its chlorination product, *chloralide* (VI).

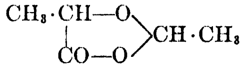
(I)



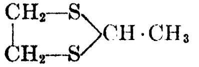
(III)



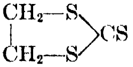
(V)



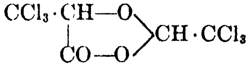
(II)



(IV)



(VI)

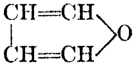


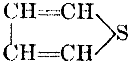
These heterocyclic compounds are closely related to aliphatic compounds, and most of them have been described in Volume I.

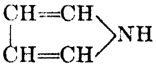
AZOLES

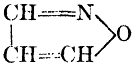
The compounds with five-membered rings containing several hetero atoms, at least one of which is nitrogen, the rest being oxygen, nitrogen, or sulfur, are called azoles (*Hantzsch,* Ann. **249**, 1; *Freund, Kuh,* Ber. **23**, 2823). The most important of the azoles are those whose hetero atoms are all nitrogen atoms, or all nitrogen atoms but one; these may be considered as being derived from furan, thiophene, and pyrrole by the replacement of methine groups by nitrogen atoms, which influences the stability of the rings very little (see p. 4).

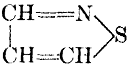
(The less common names are enclosed in brackets)

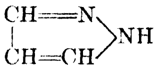

Furan

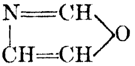

Thiophene

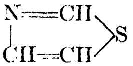

Pyrrole

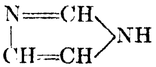

[1,2-Azoxole]
Isoxazole (p. 118)

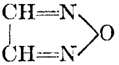

[1,2-Azthiole]
Isothiazole (p. 123)

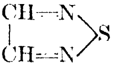

[1,2-Diazole]
Pyrazole (p. 91)

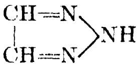

[1,3-Azoxole]
Oxazole (p. 136)

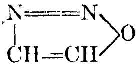

[1,3-Azthiole]
Thiazole (p. 140)

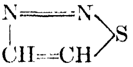

[1,3-Diazole]
Imidazole (p. 124)

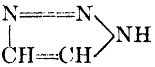

[1,2,5-Oxadiazole]
Furazan (p. 160)

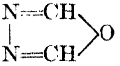

1,2,5-Thiadiazole
[Piazthiole] (p. 169)

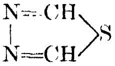

2,1,3-Triazole
[Osotriazole] (p. 147)

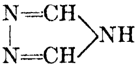

1,2,3-Oxadiazole
[Diazoxide] (p. 165)

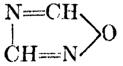

1,2,3-Thiadiazole
(p. 168)

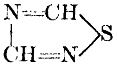

1,2,3-Triazole
(p. 147)

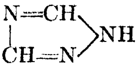

1,3,4-Oxadiazole
[Oxbiazole] (p. 163)

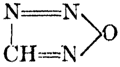

1,3,4-Thiadiazole
(p. 166)

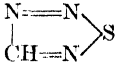

4,1,2-Triazole
(p. 153)

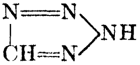

1,2,4-Oxadiazole
[Azoxime] (p. 162)

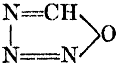

1,2,4-Thiadiazole
[Azosulfime] (p. 165)

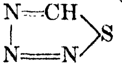

1,2,4-Triazole
(p. 153)

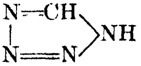

1,2,3,5-Oxatriazole


1,2,3,5-Thiatriazole


2,1,3,4-Tetrazole
(p. 169)

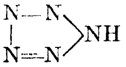

1,2,3,4-Oxatriazole
(*cf. Freund, Schwarz,*
Ber. **29**, 2492)


1,2,3,4-Thiatriazole
[Triazsulfole] (p. 169)


1,2,3,4-Tetrazole
(p. 169)

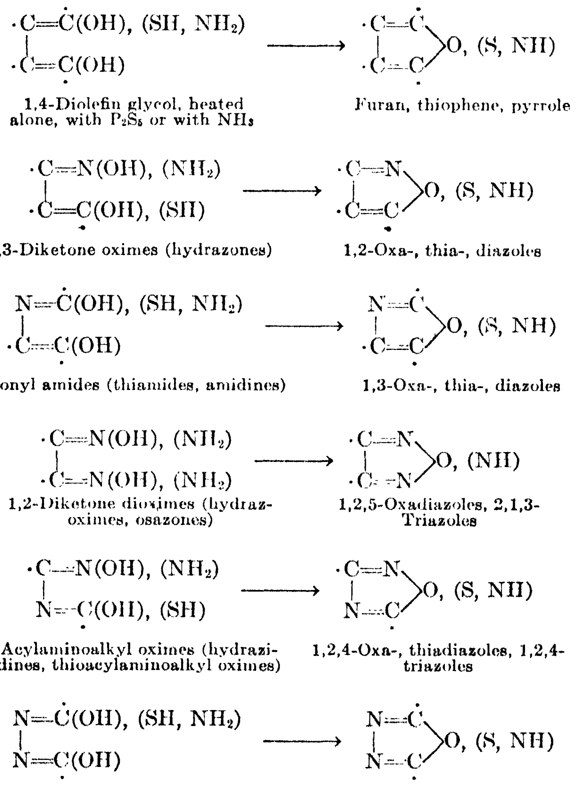
For some of these compounds trivial names, such as pyrazole and furazan, are used, but most of them are designated according to the number and kind of the hetero atoms in the ring: oxazole, thiadiazole, triazole, and so forth. In the classification on page 89 the azole ring systems obtained by replacement by nitrogen atoms of the methine groups of furan, thiophene, and pyrrole are shown. The nomenclature and numbering follow the rules given in the introduction (p. 8).

Not all of the parent compounds of these ring systems are known. In several cases only the homologues have been reported, in some, only the *benzo* derivative. The final step in the above system, the replacement of the last methine group with a nitrogen atom, which in the case of pyrrole leads to pentazole:



has not yet proved possible (*cf. Curtius*, Ber. **48**, 1614).

The general ring synthesis of the azoles, similar to that of furan, thiophene, and pyrrole, consists in the condensation of nitrogen analogues of 1,4-diketones or 1,4-diolefin glycols:



1,4-Diolefin glycol, heated alone, with P_2S_5 or with NH_3 — Furan, thiophene, pyrrole

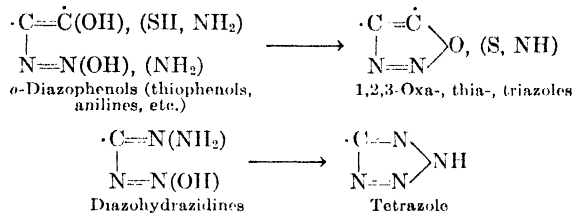
1,3-Diketone oximes (hydrazones) — 1,2-Oxa-, thia-, diazoles

Ketonyl amides (thiamides, amidines) — 1,3-Oxa-, thia-, diazoles

1,2-Diketone dioximes (hydrazoximes, osazones) — 1,2,5-Oxadiazoles, 2,1,3-Triazoles

Acylaminoalkyl oximes (hydrazidines, thioacylaminoalkyl oximes) — 1,2,4-Oxa-, thiadiazoles, 1,2,4-triazoles

s-Diacyl hydrazines, heated alone, with P_2S_5, or with NH_3 — 1,3,4-Oxa-, thiadiazoles, 4,1,2-triazoles

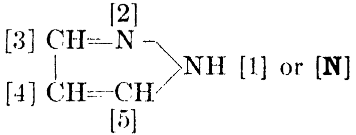

o-Diazophenols (thiophenols, anilines, etc.)
1,2,3-Oxa-, thia-, triazoles
Diazohydrazidines
Tetrazole

This schematic summary becomes clearer when considered together with the individual syntheses described in the following sections.

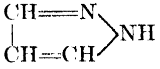
The numerous and important pyrazoles, with their benzo derivatives, the indazoles, will be described first. Next will come the isoxazoles and their benzo derivatives, the indoxazenes, followed by the imidazoles, the oxazoles, and the thiazoles, each with their benzo derivatives. In the rings containing three hetero atoms the triazoles and their benzo derivatives are first, then the four groups of oxadiazoles and the four groups of thiadiazoles. Finally the thiatriazoles and tetrazoles are discussed.

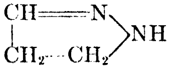
II. FIVE-MEMBERED RINGS WITH TWO HETERO ATOMS

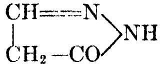
1. PYRAZOLES:

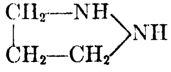


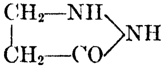
Pyrazole, $C_3H_4N_2$, has the structure of a pyrrole in which one of the methine groups adjacent to an NH-group has been replaced by a nitrogen atom. For further details of the constitution of pyrazoles, see under 3-methylpyrazole, p. 93. The dihydropyrazoles are called pyrazolines, and the tetrahydropyrazoles, pyrazolidines; oxo derivatives of the hydrogenated pyrazoles are pyrazolones, which include the febrifuges *antipyrine* and *pyramidone*, pyrazolidones, and pyrazolediones:

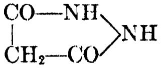

Pyrazole


Pyrazoline


Pyrazolone


Pyrazolidine

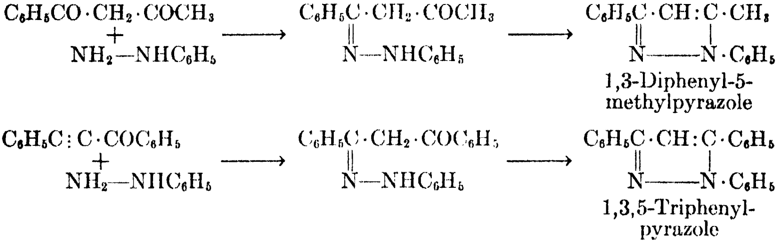

Pyrazolidone


3,5-Pyrazoledione

PYRAZOLE, m.p. 70°, b.p. 187°, is prepared: (*1*) from epichlorohydrin and hydrazine hydrate with zinc chloride (*Balbiano*, Ber. **23**, 1105; for the course of the reaction, see p. 93), (*2*) from the acetal of propiolaldehyde, $HC{:}C\cdot CH(OR)_2$, by boiling with aqueous hydrazine sulfate (*Claisen*, Ber. **36**, 3666); (*3*) from its carboxylic acid (p. 99) by decarboxylation (*Buchner, Papendieck*, Ann. **273**, 232; *Buchner, v. der Heide*, Ber. **34**, 348); (*4*) from pyrazoline (p. 101) with bromine (*Curtius*, Ber. **29**, 775); (*5*) from acetylene and diazomethane: $C_2H_2 + CH_2N_2 = C_3H_4N_2$ (*cf.* pp. 100, 102 and *v. Pechmann*, Ber. **31**, 2950); and (*6*) from monobromoethylene and diazomethane, the unstable bromopyrazoline being formed first (*Oliveri-Mandala*, Gazz. **40**, I, 117). It is a weak base, forming unstable salts. It does not add methyl iodide. Ammoniacal silver solution precipitates the silver salt $C_3H_3N_2Ag$, which corresponds to the potassium salt of pyrrole, and reacts with methyl iodide to give N-methylpyrazole (p. 94) or its methyl iodide addition product. The platinum double salt $(C_3H_4N_2 \cdot HCl)_2PtCl_4 \cdot 2H_2O$ is converted at 200–210° by loss of 4 mols of HCl to $(C_3H_3N_2)_2PtCl_2$ (*Balbiano*, Atti accad.Lincei **1892**, II, 366). **N-Acetylpyrazole,** b.p. 156°, and **N-benzoylpyrazole,** b.p. 281°, from pyrazole and acetyl chloride or benzoyl chloride (*Knorr*, Ber. **28,** 716).

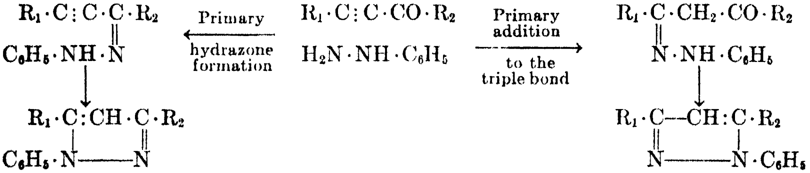
HOMOLOGUES OF PYRAZOLE are formed by these methods:

1. From the hydrazones of β-diketones and β-oxo aldehydes or hydroxymethylene ketones; these hydrazones are obtained from hydrazines and β-dioxo compounds by splitting off water or from hydrazines and α-acetylene aldehydes or ketones —C≡C—CO— by addition (*Moureu, Brachin*, C.r. **136,** 1262), but they cannot usually be isolated, since they lose water quickly to form pyrazoles:


$C_6H_5CO \cdot CH_2 \cdot COCH_3$ + $NH_2—NHC_6H_5$
$C_6H_5C \cdot CH_2 \cdot COCH_3$ / N—NHC_6H_5
$C_6H_5C \cdot CH:C \cdot CH_3$ / N———$N \cdot C_6H_5$
1,3-Diphenyl-5-methylpyrazole
$C_6H_5C:C \cdot COC_6H_5$ + $NH_2—NHC_6H_5$
$C_6H_5C \cdot CH_2 \cdot COC_6H_5$ / N—NHC_6H_5
$C_6H_5C \cdot CH:C \cdot C_6H_5$ / N———$N \cdot C_6H_5$
1,3,5-Triphenylpyrazole

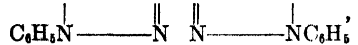
Unsymmetrical β-dioxo compounds yield two isometric pyrazoles, since both possible hydrazones are formed. In the example given above, 1,5-diphenyl-3-methylpyrazole is produced in the same reaction which gives 1,3-diphenyl-5-methylpyrazole. The formation of pyrazoles by the reaction of hydroxymethylene ketones and their derivatives with aryl and alkylhydrazines has been thoroughly unvestigated; in this reaction also, the isomeric pyrazoles are produced (*v. Auwers*, Ber. **59,** 1285; *v. Auwers, Mauss*, Ann. **452,** 182).

The reaction of unsymmetrical acetylene ketones or acetylene aldehydes with phenylhydrazine also gives two isomeric pyrazoles. Which one is formed in greater quantity depends on the first phase of the reaction, which is often not clear. It may be assumed that both the following reactions take place simultaneously:


$R_1 \cdot C:C \cdot C \cdot R_2$ / $C_6H_5 \cdot NH \cdot N$
Primary hydrazone formation
$R_1 \cdot C:C \cdot CO \cdot R_2$
$H_2N \cdot NH \cdot C_6H_5$
Primary addition to the triple bond
$R_1 \cdot C \cdot CH_2 \cdot CO \cdot R_2$ / $N \cdot NH \cdot C_6H_5$
$R_1 \cdot C:CH \cdot C \cdot R_2$ / $C_6H_5 \cdot N$———N
$R_1 \cdot C—CH:C \cdot R_2$ / N———$N \cdot C_6H_5$

Another pyrazole synthesis, analogous to this one, consists in the action of alkyl- or arylhydrazines on α-halogenated, unsaturated aldehydes, or ketones of the type R·CH:CBr·CO·R (*v. Auwers, Broche*, Ber. **55,** 3886; *v. Auwers, Schmidt*, Ber. **58,** 528).

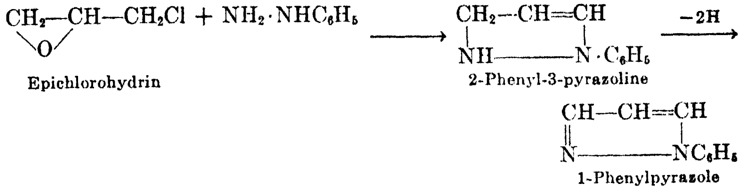
From oxalyl diketones and phenylhydrazine *diphenyldialkyl-3,3′-bipyrazoles,*



, are obtained (*Claisen, Roosen*, Ann. **278,** 295).

2. From the corresponding pyrazolecarboxylic acids (p. 100) by decarboxylation.

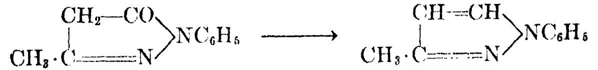
3. From pyrazolines (p. 102) by removal of two hydrogens. In many cases reactions which should produce pyrazolines give pyrazoles, as in the action of hydrazines on epichlorohydrin (*cf.* pyrazole):


Epichlorohydrin

2-Phenyl-3-pyrazoline

1-Phenylpyrazole

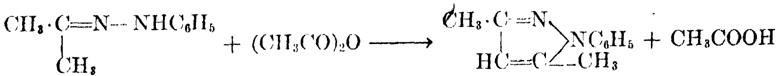
4. From pyrazolones or pyrazolidones by heating with phosphorus tribromide under pressure (*Stoermer, Martinsen,* Ann. **352,** 322) or by distillation with zinc dust or P_2S_5 (*Knorr, Duden,* Ber. **26,** 103):


1-Phenyl-3-methyl-5-pyrazolone

1-Phenyl-3-methylpyrazole

These oxo derivatives of pyrazole can also be converted by $POCl_3$ to chlorinated pyrazoles, from which the chlorine can be eliminated by reduction (*Michaelis, Röhmer,* Ber. **31,** 2907).

5. From some hydrazones of monoketones by heating with acid anhydrides:


Phenylhydrazone of acetone

1-Phenyl-3,5-dimethylpyrazole

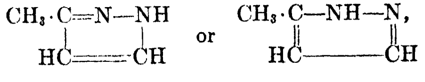
Behavior.—All homologues of pyrazole are weak bases which form double salts with silver nitrate, mercuric chloride, and platinum chloride. Like the Pt-double salt of pyrazole their Pt-double salts lose four molecules of HCl when heated, leaving R_2PtCl_2 (R = pyrazole radical). With alkyl iodides they usually form pyrazolium compounds (see p. 95).

Potassium permanganate oxidizes C-alkylpyrazoles to pyrazolecarboxylic acids, unlike the alkylpyrroles, which are destroyed by this reagent (*Knorr, Laubmann,* Ber. 22, 172). In N-phenylpyrazoles the phenyl group is often split off by oxidation, and replaced by hydrogen, especially if the phenyl group is aminated.

Reducing agents have little effect on pyrazoles with free imine groups (*Buchner, Fritsch,* Ann. **273,** 266). N-Phenylpyrazoles are reduced to pyrazolines (p. 101), which give color reactions with $FeCl_3$, chromates, and the like (*Knorr's pyrazoline reaction*); energetic reduction often splits the N—N bond, producing *1,3-propanediamine derivatives.* In several N-phenylpyrazoles reduction splits off the phenyl group as benzene or the like.

For spectroscopic data on pyrazoles, see *v. Auwers,* Ann. **437,** 36, 63.

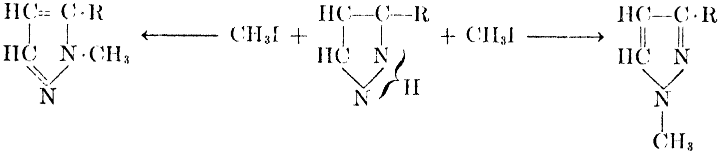
Pyrazoles with free imine hydrogens: 3(5)-**methylpyrazole:**



oil, b.p. 204°, is formed: (*1*) from hydroxymethyleneacetone and hydrazine (*v. Auwers, Broche,* Ber. **55,** 3898); (*2*) from its carboxylic acids; (*3*) from 1-phenyl-3-methylpyrazole and from 1-phenyl-5-methylpyrazole by oxidative removal of the phenyl group (*Knorr,* Ann. **279,** 217). Since it is impossible to obtain the isomeric 3-methyl and 5-methyl derivs. from the corresponding 1-phenylmethylpyrazoles, it must be concluded that in pyrazoles with free imine groups the 3- and the 5-positions are equivalent. To explain this, Knorr assumes that pyrazole, like benzene, contains "movable bonds," so that the imine H oscillates between the two N atoms (*Knorr,* Ann. **279,** 188; *cf. Buchner, v. d. Heide,* Ber. **35,** 31). **3,5-Dimethylpyrazole,** $\overline{NH\cdot N:C(CH_3)\cdot CH:C}(CH_3)$, m.p. 107°, b.p. 220° from acetylacetone with hydrazine, and from 1-phenyl-3,5-dimethylpyrazole by reduction (*removal of the phenyl group: Marchetti,* Atti accad.Lincei **1891, II, 372;** *Bladin,* Ber. **25,** 744). **3,4-Dimethylpyrazole,** m.p. 58°, from hydroxymethylene-ethyl methyl ketone and hydrazine sulfate (*v. Auwers, Kohlhaas*, Ann. **437**, 36).

3,4,5-Trimethylpyrazole, $NH{-}N{=}C(CH_3){-}C(CH_3){=}C(CH_3)$, m.p. 138°, b.p. 233°, from methylacetylacetone. **3,4,4,5-Tetramethylpyrazole**, $N{=}C(CH_3){-}C(CH_3)_2{-}C(CH_3){=}N$, m.p. 50–55°, b.p. 243°, from dimethylacetylacetone, is derived from the methylene form, which is rare in the pyrazole series (*Oettinger*, Ann. **279**, 244; *Knorr, Oettinger*, Ann. **279**, 247). **3(5)-Phenylpyrazole**, m.p. 78°, is prepared from benzoylacetaldehyde, from its carboxylic acid and from the corresponding phenylpyrazoline (p. 102) (*Knorr*, Ber. **28**, 696; *Buchner, Hachumian*, Ber. **35**, 37, 42); the isomeric 4-**phenylpyrazole**, m.p. 228°, is obtained from the corresponding phenylpyrazoline or from its dicarboxylic acid (p. 100 and *Behaghel, Buchner*, Ber. **35**, 34). **3,5(5,3)-Phenylmethylpyrazole**, m.p. 128°, b.p. 317°, from benzoylacetone (*Sjollema*, Ann. **279**, 248) or from acetylphenylacetylene (*Moureu, Brachin*, C.r. **136**, 1262) or from phenylmethylisoxazole (p. 120) by heating with alcoholic NH_3 (*Goldschmidt*, Ber. **28**, 2952).

N-*Alkyl*- and N-*arylpyrazoles* are prepared either by alkylation of pyrazoles with free imine hydrogen, which is accomplished by treatment of their alkali or silver salts with alkyl iodides, dimethyl sulfate, or methyl *p*-toluenesulfonate, or by the action of alkyl- and arylhydrazines on 1,3-dioxo compounds (see p. 92). Because of the equivalence of the two nitrogen atoms in pyrazole, alkylation of a 3-substituted pyrazole results in the formation of both a 1,3- and a 1,5-disubstituted derivative:



1,5-Derivative 1,3-Derivative

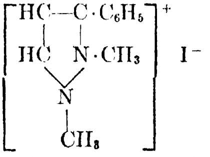
The ratio of the yields of the two products is greatly influenced by the substituents already present in the ring (*v. Auwers, Hollmann*, Ber. **59**, 601, 1282; *Rojahn*, Ber. **59**, 607; *v. Auwers, Stuhlmann*, Ber. **59**, 1043; *v. Auwers, Bahr*, J.pr. **116**, 65). For the determination of constitution the molecular refraction is useful, since the specific exaltation (E) is consistently lower for a 1,5-derivative than for a 1,3-derivative, especially if one substituent is phenyl [*v. Auwers, Ernst*, Z.physik. Chem. **122** (1926), 217].

N-ALKYLPYRAZOLES: **1-Methylpyrazole**, b.p. 127°, from the silver salt of pyrazole and methyl iodide (*Buchner*, Ann. **273**, 214; *Knorr*, Ber. **28**, 716); **1,3-dimethylpyrazole**, b.p. 136° (*v. Auwers, Broche*, Ber. **55**, 3898); **1,3,5-trimethylpyrazole**, $(CH_3)_2C_3HN_2CH_3$, m.p. 37°, b.p. 170°. **1,3,4-Trimethylpyrazole**, m.p. 118° (*v. Auwers, Kohlhaas*, Ann. **437**, 36). **1-Ethyl-3,5-dimethylpyrazole**, b.p. 172° (*v. Auwers, Daniel*, J.pr. **110**, 249). **1-Ethyl-5-methylpyrazole**, b.p. 161°, and **1-ethyl-3-methylpyrazole**, b.p. 152°, from the corresponding 3- or 5-carboxylic acids (*v. Auwers, Hollmann*, Ber. **59**, 606; *v. Auwers, Mausolf*, Ber. **60**, 1730). **1,3,5-Trimethylpyrazole** and **1,3,4,5-tetramethylpyrazole**, $(CH_3)_3$-$C_3N_2{\cdot}CH_3$, b.p. 190–193°, are prepared from acetylacetone and methylacetylacetone with methylhydrazine (*Knorr*, Ann. **279**, 232, 235). **1-Methyl-5-phenylpyrazole**, b.p. 118° (12 mm.); **1-methyl-3-phenylpyrazole**, m.p. 56°, b.p. 138° (12 mm.) (*v. Auwers, Mausolf*, Ber. **60**, 1730). **1-Ethyl-5-phenylpyrazole**, b.p. 129° (12 mm.); **1-ethyl-3-phenylpyrazole**, b.p. 146° (12 mm.).

N-PHENYLPYRAZOLES: **1-Phenylpyrazole**, m.p. 11°, b.p. 246°, d = 1.1125, is obtained from epichlorohydrin or the acetal of propiolaldehyde (*Claisen*, Ber. **36**, 3666) with phenylhydrazine (see above), or from 1-phenylpyrazolone or its carboxylic acids; on reduction it yields phenylpyrazoline and N-phenyltrimethylenediamine. **1-Tolylpyrazole**, m.p. 33°, b.p. 259°, reduces to N-tolyltrimethylenediamine (*Balbiano*, Gazz. **18**, 354). **1-Phenyl-3-methylpyrazole**, $C_6H_5{\cdot}N{-}N{=}C(CH_3){-}CH{=}CH$, m.p. 37°, b.p. 255°, methyl iodide addition product, m.p. 144°, from phenylmethylpyrazolone (see p. 104 and *Knorr*, Ann. **238,** 203; *Andreocci,* Atti accad.Lincei **1898,** I, 269), and from hydroxymethyleneacetone, together with the isomeric **1-phenyl-5-methylpyrazole,** $C_6H_5N{-}N{=}CH{-}CH{=}C(CH_3)$, oil, b.p. 263°, methyl iodide addition product, m.p. 256° (*Stoermer, Martinsen,* Ann. **352,** 333). **1-Phenyl-4-methylpyrazole,** $C_6H_5N{-}N{=}CH{-}C(CH_3){=}CH$, b.p. 266°, from the methyl iodide addition product of 1-phenylpyrazole by rearrangement (*Balbiano, Marchetti,* Atti accad. Lincei, **1893,** I, 114). **1-Phenyl-3,5-dimethylpyrazole,** b.p. 273°, from acetylacetone, when reduced yields benzene and dimethylpyrazole (page 93), besides 1-tetrahydrophenyl-3,5-dimethylpyrazole; the latter decomposes on oxidation to dimethylpyrazole and adipic acid (*Marchetti,* Atti accad.Lincei, **1893,** I, 44). **1-Phenyl-3,4-dimethylpyrazole,** b.p. 285°, from 1-phenyl-3,4-dimethylpyrazolone (*Stoermer, Martinsen,* Ann. **352,** 330), and from hydroxymethyleneëthyl methyl ketone, $CH(OH){:}C(CH_3){\cdot}CO{\cdot}CH_3$, (*v. Auwers, Kohlhaas,* Ann. **437,** 36). **1-Phenyl-4,5-dimethylpyrazole,** b.p. 141 (11 mm.) (*v. Auwers, Kohlhaas,* Ann. **437,** 36). **1-Phenyl-3,4,5-trimethylpyrazole,** b.p. 287 290° (*McConnan,* Ber. **37,** 3525). **1,3-Diphenylpyrazole,** m.p. 56°, b.p. 337°, from benzoylacetaldehyde (*Claisen, Fischer,* Ber. **21,** 1135); **1,5-diphenylpyrazole,** m.p. 54°, b.p. 340°, from its carboxylic acid (*Bischler,* Ber. **25,** 3145). Both **1,3-diphenyl-5-methylpyrazole,** and **1,5-diphenyl-3-methylpyrazole** occur in a labile and a stable form, m.p. 47° and 77°, and m.p. 63° and 72°; this isomerism is a polymorphism (*v. Auwers, Schaum,* Ber. **62,** 1671). **1,3,5-Triphenylpyrazole,** m.p. 140°, from dibenzoylmethane or benzoylphenylacetylene (*Moureu, Brachin,* C.r. **136,** 1262; *Knorr, Laubmann,* Ber. **21,** 1205), or from its 4-carboxylic acid by heating (*Minunni, d'Urso,* Gazz. **58,** 691). **1,4,5-Triphenylpyrazole,** m.p. 212°, from its carboxylic acid (*Bischler,* Ber. **26,** 1881). For the formation of **1,3,4-triphenylpyrazole,** m.p. 185°, by the decomposition of 1,3,4,6-tetraphenyldihydropyridazine, see *Smith,* Ann. **289,** 332.

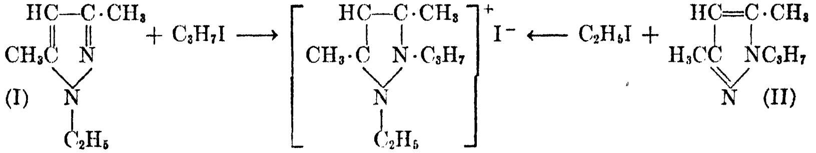
N-ACYLPYRAZOLES are obtained from the acid chlorides of the corresponding acids and the free pyrazole or its Na or Ag salt. The acylation of 3(5)-alkylpyrazoles is analogous to their alkylation (see above, and *v. Auwers,* J.pr. **110,** 153).

N,N-DIALKYL- or N-ARYL-N-ALKYLPYRAZOLIUM COMPOUNDS. Alkyl halides react with 1-alkyl- or 1-arylpyrazoles to form 1,2-dialkyl- or 1-aryl-2-alkylpyrazolium compounds. The resulting compound is a typical quaternary ammonium compound:



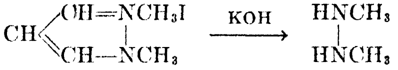
1,2-Dimethyl-3-phenylpyrazolium iodide

This method of writing the formula also indicates that the identical quaternary pyrazolium salt is obtained from propyl iodide and 1-ethyl-3,5-dimethylpyrazole (I) and from ethyl iodide and 1-propyl-3,5-dimethylpyrazole (II) (*v. Auwers, Daniel,* J.pr. **110,** 153):



When the pyrazolium compound is heated, that N-alkyl group which is less firmly bound is split off as alkyl halide. The strength of the N-alkyl bond increases in this order: allyl, benzyl, ethyl, methyl. This reaction can be used for the preparation of certain N-alkylpyrazoles, but difficulties are encountered in many cases. If the two alkyl groups on the nitrogen atoms are held with approximately the same energy, both split off, leaving a mixture of products; also, the alkyl groups are apt to wander during the reaction (*v. Auwers, Broche*, Ber. **55**, 3888). Thus, when 1-benzyl-2,3-dimethylpyrazolium iodide is heated, 1,3-dimethylpyrazole is obtained, instead of the expected 1,5-derivative.

The methyl iodide addition products of N-alkyl- and N-arylpyrazoles decompose when boiled with aqueous potassium hydroxide solution, giving symmetrical dialkylhydrazines (*Knorr, Köhler*, Ber. **39**, 3257; *Knorr, Weidel*, Ber. **42**, 3523):



HALOGEN-, NITRO-, NITROSO-, AMINO- and **BENZENEAZOPYRAZOLES, PYRAZOLESULFONIC ACIDS.** Pyrazole and its homologues have a decidedly "aromatic" character, which is apparent in their tendency to substitution reactions similar to those in the benzene series (see also pyrazole ketones). Halogen replaces the hydrogen atoms of pyrazole; bromine substitutes most readily, attacking the 4-position first. Chloropyrazoles are also formed by the action of phosphorus oxychloride on pyrazolones.

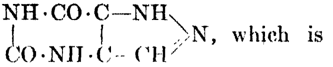
When pyrazole is sulfonated or nitrated, the nitro or sulfo groups enter the pyrazole nucleus. N-Phenylpyrazoles are nitrated and sulfonated in the phenyl nucleus. N-Nitrophenyl- and N-sulfophenylpyrazoles are also prepared by using nitrophenyl- and sulfophenylhydrazines in the pyrazole synthesis (*Claisen, Roosen*, Ann. **278**, 296). In the nitropyrazoles, the basic nature of pyrazole is offset by the acidity of the substituting group; these compounds are acids, and form stable salts with sodium, potassium, and other metals.

Nitropyrazoles are reduced to aminopyrazoles, which are somewhat similar to aromatic amines in behavior. Aminopyrazoles are also obtained from the hydrazides, azides, and urethanes of pyrazolecarboxylic acids by the *Curtius reaction* (Vol. I), and by the action of hydrazines on the nitriles of β-oxocarboxylic acids, α,β-acetylenecarboxylic acids (*Moureu, Lazennec*, C.r. **143**, 1239) and malononitrile. Nitroso- and benzeneazopyrazoles are synthesized from isonitroso- and benzeneazo-β-diketones with hydrazines.

4-Chloropyrazole, m.p. 77°, is formed by the action of sulfuryl chloride on pyrazole in ether (*Mazzara, Borgo*, Atti accad.Lincei [5] **15**, I, 704). **4-Bromopyrazole,** m.p. 97°; **1,3,5-triphenyl-4-bromopyrazole,** m.p. 142°; **3-methyl-5-chloropyrazole,** m.p. 116°, b.p. 138° (15 mm.), from the corresponding pyrazolone with $POCl_3$ (*v. Auwers, Niemeyer*, J.pr. **110**, 179), N-alkyl derivatives (*loc. cit.*, p. 164); **1-phenyl-3,4,5-tribromopyrazole,** m.p. 107°; **4-iodopyrazole,** m.p. 108° from pyrazole-4-diazonium chloride and KI (*Buchner*, Ann. **273**, 214; *Knorr*, Ber. **37**, 3522); **1-phenyl-4-chloropyrazole,** m.p. 76° (*Wolff, Fertig*, Ann. **313**, 21); **3-phenyl-5-chloropyrazole,** m.p. 142° (*Michaelis*, Ann. **352**, 159), alkyl derivatives (*v. Auwers, Mauss*, J.pr. **110**, 221), acyl derivatives (*loc. cit.*, p. 229); **1-phenyl-5-chloropyrazole, 1-phenyl-3-methyl-5-chloropyrazole,** b.p. 142° (9 mm.), and **1-phenyl-3,5-dichloropyrazole,** m.p. 26°, b.p. 171° (16 mm.), from 1-phenyl-5-pyrazolone, 1-phenyl-3-methyl-5-pyrazolone, and phenylhydroxypyrazolone (*Michaelis, Röhmer*, Ber. **31**, 3003; *Michaelis*, Ann. **320**, 28). **1-Phenyl-5-methyl-3-chloropyrazole,** b.p. 170° (15 mm.), from 1-phenyl-5-methyl-3-pyrazolone (p. 108).

4-Nitropyrazole, m.p. 162°, is synthesized from hydrazine and nitromalonaldehyde; **1-phenyl-4-nitropyrazole,** m.p. 127°, is synthesized from phenylhydrazine and nitromalonaldehyde [*Hill, Torrey*, Am. Chem. J. **22** (1899), 89]. **3-Methyl-4-nitropyrazole,** m.p. 134°, b.p. 325°, from methylpyrazole or 3-methyl-5-pyrazolecarboxylic acid with nitric acid-sulfuric acid (*Knorr*, Ann. **279**, 228). **4-Nitro-1,3,5-trimethylpyrazole,** m.p. 57°. **3,5-Dimethyl-4-nitrosopyrazole,** blue needles, m.p. 128°, and **1-phenyl-3,5-dimethyl-4-nitrosopyrazole,** green platelets, m.p. 94°, are prepared from isonitrosoacetylacetone (Vol. I) with hydrazine and phenylhydrazine; the second compound is oxidized by nitric acid to **1-phenyl-3,5-dimethyl-4-nitropyrazole,** m.p. 103° (*Wolff*, Ann. **325**, 192; *Sachs, Alsleben*, Ber. **40**, 664).

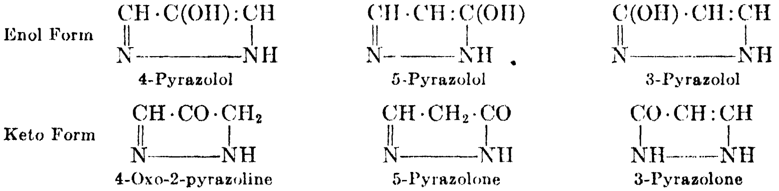
4-Aminopyrazole, m.p. 81°, readily sublimable, is obtained by reduction of 4-nitropyrazole with zinc dust and acetic acid, and by the decomposition of 1-

pyrazolo[4,3-*d*]pyrimidine-5,7(4,6)-dione,  $\begin{array}{l}NH\cdot CO\cdot C{-}NH\diagdown \\ |\qquad\quad\ \ | \qquad\quad\ \ >N \\ CO\cdot NH\cdot C{-}CH\diagup\end{array}$, which is obtained from aminomethyluracil with N_2O_3 (*Wollers*, Ann. **323**, 281; *Knorr*, Ber. **37**, 3520); it is also prepared from the *ethyl ester of 4-aminopyrazole-3,5-dicarboxylic acid*, m.p. 144° (*Bertho, Nüssel*, Ann. **457**, 288), by saponification and decarboxylation. It is readily soluble in water, the solution, especially if it is made alkaline, rapidly absorbs oxygen from the air, turning dark; picrate, m.p. 196°. 3(5)-**Aminopyrazole**, b.p. 282°, and 3,5-**diaminopyrazole**, dibenzoate m.p. 207°, which are obtained from the pyrazolecarboxylic acid azides, are more stable than the 4-amino derivative. 1-**Phenyl-3-methyl**-5-**aminopyrazole, m.p.** 116°, is formed from acetylacetonitrile and phenylhydrazine, and also from antipyrine chloride by heating with ammonium carbonate (*Michaelis*, Ann. **339,** 134). 1-**Phenyl**-3-**ethyl**-4-**methyl**-5-**aminopyrazole,** m.p. 81°, from α-propionylpropionitrile, $C_2H_5COCH(CH_3)CN$, and phenylhydrazine. 4-**Amino**-1,3,5-**trimethylpyrazole,** m.p. 103°, by reduction of nitrotrimethylpyrazole. Nitrous acid converts aminopyrazoles into stable diazonium salts, which do not decompose in boiling water; like the aromatic diazonium salts, they couple with aromatic amines, phenols, and the like to form azo dyes.

Other benzeneazopyrazoles, such as 1-**phenyl**- and 1-**phenyl-5-methyl-4-benzeneazopyrazole,** $C_6H_5N:NC_3H_2N_2\cdot C_6H_5$, m.p. 124°, and $C_6H_5N:NC_3H(CH_3)N_2\cdot C_6H_5$, m.p. 112°, have been synthesized from the benzeneazo derivatives of malondialdehyde and of acetylacetaldehyde with phenylhydrazine; 1-**phenyl-3-methyl-4-benzeneazopyrazole,** m.p. 126°, from phenylmethylbenzeneazopyrazolone (p. 105) (*Michaelis, Leonhardt*, Ber. **36**, 3597; *Claisen*, Ber. **36**, 3669). 1,5-**Diphenyl**-3-**methyl**-4-**benzeneazopyrazole,** m.p. 136°, from phenylmethyltriketone (Vol. III) with phenylhydrazine (*Sachs, Röhmer*, Ber. **35**, 3317). 1-**Phenyl**-3-**methyl**-5-**benzeneazopyrazole,** m.p. 62°, from phenylhydrazinopyrine (p. 107), by oxidation with HgO and subsequent heating (*Michaelis, Kobert*, Ber. **42**, 2765).

Methylpyrazolesulfonic acid, $C_3H_2N_2(CH_3)(SO_3H)$, m.p. 258°, from methylpyrazole and fuming sulfuric acid (*Knorr*, Ann. **279**, 230).

PYRAZOLOLS. The pyrazolols are desmotropic with the oxopyrazolines or pyrazolones (p. 103):

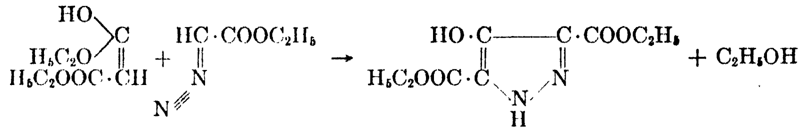


$$\begin{array}{lccc} \text{Enol Form} & \begin{array}{l}CH\cdot C(OH):CH\\ \|\qquad\qquad\quad |\\ N{-}{-}{-}{-}{-}NH\end{array} & \begin{array}{l}CH\cdot CH:C(OH)\\ \|\qquad\quad\ \ |\\ N{-}{-}{-}NH\end{array} , & \begin{array}{l}C(OH)\cdot CH:CH\\ \|\qquad\qquad\quad |\\ N{-}{-}{-}{-}{-}NH\end{array} \\ & \text{4-Pyrazolol} & \text{5-Pyrazolol} & \text{3-Pyrazolol} \\ \text{Keto Form} & \begin{array}{l}CH\cdot CO\cdot CH_2\\ \|\qquad\quad |\\ N{-}{-}{-}NH\end{array} & \begin{array}{l}CH\cdot CH_2\cdot CO\\ \|\qquad\quad |\\ N{-}{-}{-}NH\end{array} & \begin{array}{l}CO\cdot CH:CH\\ |\qquad\quad\ \ |\\ NH{-}{-}{-}NH\end{array} \\ & \text{4-Oxo-2-pyrazoline} & \text{5-Pyrazolone} & \text{3-Pyrazolone} \end{array}$$

The hydroxyl form of 4-pyrazolol appears to be the more stable one, since it gives, especially in aqueous solution, the reactions typical of enols (*Bertho, Nüssel*, Ann. **457**, 294), and is readily converted by phenyl isocyanate to a urethan, and by benzoyl chloride to a benzoic acid ester. On the other hand, with diazonium compounds and with N_2O_3 it forms benzeneazo and isonitroso compounds (*Wolff*, Ann. **313**, 1). With alkylating agents 3- and 5-pyrazolones yield, besides the isomeric N-alkyl derivatives (antipyrines), alkoxypyrazoles; with acid halides they give esters of pyrazolols. With alkyl iodides the alkoxypyrazoles form addition products, which are identical with those obtained from antipyrines and alkyl iodides; when warmed alone or with alkali, these products are converted to antipyrines. The esters of pyrazolols also give alkyl iodide addition products which decompose to antipyrines (*Himmelbauer*, J.pr. **54**, 177; *Stolz*, J.pr. **55**, 145; *Knorr, Rabe*, Ann. **293**, 42; see also *Michaelis, Pasternack*, Ber. **32**, 2399). Alkoxypyrazoles are also prepared by the splitting off of water from the hydrazones of β-oxo carboxylic acid esters with special reagents.

For 3- and 5-pyrazolols, see under pyrazolones.

4-PYRAZOLOLS can be prepared by the action of aliphatic diazo compounds, especially diazoacetic ester, on compounds which enolize readily, such as the diethyl ester of malonic acid (*Bertho, Nüssel*, Ann. **457**, 284):



4-Hydroxypyrazole-3,5-dicarboxylic acid ester

This reaction is analogous to the formation of pyrazolines from ethylene derivatives and diazoacetic ester, and to the synthesis of 1,2,3-triazol-5-ols from phenylazide and malonic ester.

4-Pyrazolol, m.p. 118°, from its carboxylic acid (p. 109), reacts with methyl iodide to give the methyl iodide addition product of 1-methyl-4-pyrazolol. **1-Phenyl-4-pyrazolol**, m.p. 120°, from its carboxylic acid (p. 110), is converted by phenyl isocyanate to the corresponding carbamic acid ester, m.p. 168°. **3,5-Dimethyl-** and **3-phenyl-5-methyl-4-pyrazolol**, m.p. 173° and 188°, from dimethyl- and phenylmethyltriketone with hydrazine (*Sachs*, *Röhmer*, Ber. **35**, 3313, 3318). **4-Hydroxypyrazole-3,5-dicarboxylic acid diethyl ester**, m.p. 151° (see above), saponifies to 4-hydroxypyrazole-5-carboxylic acid, m.p. 204° (*Bertho*, *Nüssel*, Ann. **457**, 288).

5-ALKOXYPYRAZOLES: **1-Phenyl-5-ethoxypyrazole** is prepared from its carboxylic acid ester, which is obtained by the condensation of the phenylhydrazone of oxaloacetic acid ester with $ZnCl_2$; saponification of the ethoxy group with HCl converts this compound to 1-phenylpyrazolone, m.p. 118° (p. 104) (*Stolz*, Ber. **27**, 407). **1-Phenyl-3-methyl-5-methoxypyrazole**, b.p. 240°, is obtained from phenylmethylpyrazolone (p. 105) with diazomethane (*v. Pechmann*, Ber. **28**, 1626), or with methyl iodide and sodium methylate, together with the isomeric antipyrine (p. 106) (reaction mechanism: *Backer*, *Meyer*, Rec. **45**, 428); also from the methyl ester of acetoacetic acid with phenylhydrazine and hydrochloric acid. When heated to 250° it rearranges to antipyrine (Ger. Pat. 95643, 1897). Its methyl iodide addition product, which is also obtained from antipyrine and methyl iodide, is converted immediately by boiling sodium hydroxide solution to antipyrine (p. 106 and *Knorr*, Ann. **293**, 17). **1-Phenyl-3-methyl-5-ethoxypyrazole**, m.p. 38°, b.p. 301°, from the phenylhydrazone of acetoacetic ester with acetyl chloride or excess hydrochloric acid, is converted by saponification to phenylmethylpyrazolone (see above), and by reduction with sodium and alcohol to phenylmethylpyrazoline (*Stolz*, Ber. **28**, 627, 635; *Knorr*, Ber. **28**, 706). The last two ethers are also formed by decarboxylation of **phenylmethylcarbethoxy-** and **-carbomethoxypyrazolone**, which result from the action of the ethyl and methyl ester of chloroformic acid on phenylmethylpyrazolone (see above, and *Himmelbauer*, J.pr. **54**, 180; *Stolz*, J.pr. **55**, 149).

1-Phenyl-5-methyl-3-methoxypyrazole, b.p. 274°, from 1-phenyl-5-methyl-3-pyrazolone with methyl iodide and sodium methylate (*Prager*, Ann. **338**, 282).

Pyrazolecarboxaldehydes are prepared by catalytic reduction of the corresponding acid chlorides (according to *Rosenmund*, Ber. **54**, 425; Vol. I, p. 226); 3- and 5-carboxaldehydes of 1-alkyl and 1-phenylpyrazoles are relatively easy to obtain, but the 4-carboxaldehyde is formed in very small yield (*Rojahn*, *Fahr*, Ann. **434**, 252; *Rojahn*, *Seitz*, Ann. **437**, 297).

1-Phenylpyrazole-5-carboxaldehyde, oil; semicarbazone, m.p. 168°; oxime, m.p. 177°. **1-Phenyl-5-methylpyrazole-3-carboxaldehyde**, b.p. 185° (22 mm.); semicarbazone, m.p. 183°; oxime, m.p. 166°. **1-Phenyl-3-methylpyrazole-5-carboxaldehyde**, oil; oximes, m.p. 146°, 179°. **1,5-Dimethylpyrazole-3-carboxaldehyde**, m.p. 56°, b.p. 120° (13 mm.); semicarbazone, m.p. 201°; oxime, m.p. 178°. **1,3-Dimethylpyrazole-5-carboxaldehyde**, b.p. 83° (12 mm.); semicarbazone, m.p. 206°; oxime, m.p. 148°. **1,4-Dimethylpyrazole-3-carboxaldehyde**, m.p. 127°; semicarbazone, m.p. 216°.

PYRAZOLE KETONES are prepared similarly to the thiophene, pyrrole, and indole ketones:

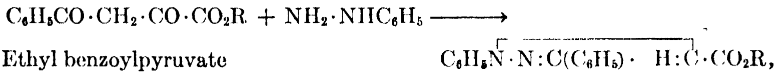
1. By heating pyrazoles with acid chlorides (*Michaelis*, *Rojahn*, Ber. **50**, 737; *Rojahn*, Ber. **55**, 291): **1-Phenyl-4-acetylpyrazole**, m.p. 122°; oxime, m.p. 130°; phenylhydrazone, m.p. 143° (dec.). **1-Phenyl-4-benzoylpyrazole**, m.p. 123°; oxime, m.p. 143°; phenylhydrazone, m.p. 139° (dec.).

2. By ring synthesis from 1,3-diketones with suitable aliphatic diazo compounds (*cf.* methods *2* and *4* for pyrazolecarboxylic acids): **4-Methyl-5-acetylpyrazole,** b.p. 161° (26 mm.), from its carboxylic acid (see below). **4-Methyl- and 4-phenyl-3,5-diacetylpyrazole,** m.p. 114° and 134°, from the diazo anhydride of acetylacetone (Vol. I) with acetylacetone or benzoylacetone (*Wolff*, Ann. **325,** 185).

PYRAZOLECARBOXYLIC ACIDS are produced:

1. By oxidation of alkylpyrazoles with potassium permanganate. If more than one alkyl group is present, each one is oxidized in turn.

2. By the ring-closure of carboxylic acid esters of β-diketones or hydroxymethylene ketones with hydrazines (*Mumm, Bergell,* Ber. **45,** 3045):



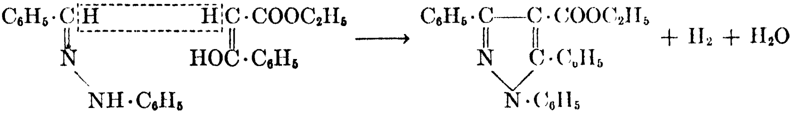
$$C_6H_5CO\cdot CH_2\cdot CO\cdot CO_2R + NH_2\cdot NHC_6H_5 \longrightarrow C_6H_5N\cdot N{:}C(C_6H_5)\cdot\ H{:}C\cdot CO_2R,$$

Ethyl benzoylpyruvate

1,3-Diphenylpyrazole-5-carboxylic acid ester

γ-Dioxocarboxylic acid esters, such as acetonyl- and phenacylacetoacetic ester and acetoacetylsuccinic acid ester, react with benzenediazonium salts to give phenylhydrazones of β-dioxocarboxylic acid esters, which condense to pyrazolecarboxylic acid esters (*Bischler,* Ber. **26,** 1881; *Bülow, Schlesinger,* Ber. **32,** 2880; *Stolz,* Ber. **33,** 262; *Bülow, Baur,* Ber. **58,** 1926).

3. By the reaction of phenylhydrazones of aldehydes with β-oxocarboxylic acid esters in the presence of zinc chloride (*Minunni,* Atti accad.Lincei [5] **14,** II, 414; Gazz. **55,** 502; *Minunni, d'Urso,* Gazz. **58,** 691):



$$\begin{array}{l} C_6H_5\cdot CH \quad HC\cdot COOC_2H_5 \\ \quad \| \qquad\qquad\qquad \| \\ \quad N \qquad\qquad HOC\cdot C_6H_5 \\ \quad\ \ \backslash \\ \quad NH\cdot C_6H_5 \end{array} \longrightarrow \begin{array}{l} C_6H_5\cdot C\text{—}C\cdot COOC_2H_5 \\ \quad \| \qquad \| \\ \quad N \quad C\cdot C_6H_5 \\ \quad\ \ \diagdown\diagup \\ \quad\ \ N\cdot C_6H_5 \end{array} + H_2 + H_2O$$

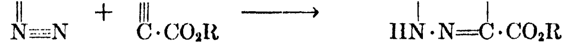
Phenylhydrazone of benzaldehyde

Benzoylacetic ester

1,3,5-Triphenylpyrazole-4-carboxylic acid ester

This method illustrates the great tendency toward formation of the pyrazole ring.

4. By addition of diazoacetic ester to mono- and dicarboxylic acids of the acetylene series (*Buchner,* Ber. **22,** 2165; Ann. **273,** 222):



$$\begin{array}{l} RO_2C\cdot CH \\ \qquad \| \\ \qquad N{\equiv}N \end{array} + \begin{array}{l} C\cdot CO_2R \\ ||| \\ C\cdot CO_2R \end{array} \longrightarrow \begin{array}{l} RO_2C\cdot C{=\!=}C\cdot CO_2R \\ \qquad | \qquad\ \ | \\ HN\cdot N{=}C\cdot CO_2R \end{array}$$

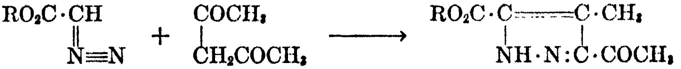
Diazoacetic ester

Acetylene-dicarboxylic acid ester

Pyrazole-3,4,5-tricarboxylic acid ester

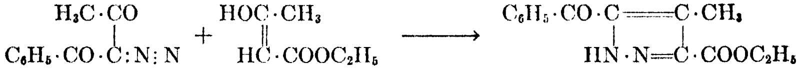
(*a*) Monohalogen substitution products of the acrylic and fumaric acid series and α,β-dihalogen substituted saturated acids, such as α,β-dibromopropionic acid and α,β-dibromosuccinic acid, react with diazoacetic ester in the same way as the acids of the acetylene series.

(*b*) Diazoacetic ester adds to β-diketones, such as acetylacetone, when warmed in sodium hydroxide solution, to form compounds such as **4-methyl-5-acetylpyrazole-3-carboxylic acid ester,** m.p. 198° (*Klages, Rönneburg,* Ber. **36,** 1128):



$$\begin{array}{l} RO_2C\cdot CH \\ \qquad \| \\ \qquad N{\equiv}N \end{array} + \begin{array}{l} COCH_3 \\ | \\ CH_2COCH_3 \end{array} \longrightarrow \begin{array}{l} RO_2C\cdot C{=\!=}C\cdot CH_3 \\ \qquad | \qquad\ \ | \\ NH\cdot N{:}C\cdot COCH_3 \end{array}$$

(*c*) The diazo anhydrides of β-diketones (*cf.* 1,2,3-oxadiazoles), which are decomposed by aqueous sodium hydroxide to a carboxylic acid and an aliphatic diazo compound, react similarly with β-diketones or β-oxo carboxylic acid esters to form diacylpyrazoles (page 99) or acylpyrazolecarboxylic acid esters (***Wolff***, Ann. **325**, 177):



Acetylbenzoyldiazomethane (a diazo anhydride)

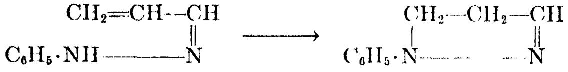
4-Methyl-5-benzoylpyrazole-3-carboxylic acid ester

The pyrazolecarboxylic acids lose CO_2 when heated. A carboxylic acid group in the 3-position is split off first, then one in the 5-position; one in the 4-position, which is not adjacent to a nitrogen atom, is most firmly bound (*Claisen*, Ann. **278**, 273).

3(5)-**Pyrazolecarboxylic acid**, m.p. 209° (dec.), is obtained from 3-methyl- or 1-phenyl-3-methylpyrazole (p. 94) by oxidation, and from 3,5-pyrazolinedicarboxylic acid by decarboxylation and dehydrogenation (*Buchner*, *Papendieck*, Ann. **273**, 237; *v. Pechmann*, *Burkard*, Ber. **33**, 3595). 4-**Pyrazolecarboxylic acid**, m.p. 275°, from pyrazoletricarboxylic acid, or from 4-(nitrophenyl)pyrazole (*Behaghel*, *Buchner*, Ber. **35**, 34). 3,5-**Pyrazoledicarboxylic acid**, m.p. 289°, from methylpyrazolecarboxylic acid, dimethylpyrazole (*Knorr*, Ann. **279**, 218; *Marchetti*, Atti accad.Lincei **1892**, I, 356), and dibromopropionic acid ester with diazoacetic ester. 4,5-**Pyrazoledicarboxylic acid**, m.p. 260° (dec.), is formed by oxidation of triacetyldihydroxy-1-naphtho[2,3]pyrazoledione, which is obtained from diacetylnaphthazarin and diazomethane (*cf.* p. 117 and *v. Pechmann*, *Seel*, Ber. **32**, 2299). 3,4,5-**Pyrazoletricarboxylic acid**, m.p. 233°, prepared according to methods *1* and *4*, and also from pyrazolinetricarboxylic acid ester (p. 102) with bromine.

3-**Methyl**-5-**pyrazolecarboxylic acid**, m.p. 236° (*Knorr*, Ann. **279**, 217; alkylation of the ethyl ester: *v. Auwers*, *Hollmann*, Ber. **59**, 601; *Rojahn*, Ber. **59**, 607). For 4,3- and 3,4-**methylpyrazolecarboxylic acid**, *v. Pechmann*, *Burkard*, Ber. **33**, 3592, 3598. 3,5-**Dimethyl**-4-**pyrazolecarboxylic acid**, m.p. 290° (dec.), from acetyl- or ethylideneacetoacetic ester (*Rosengarten*, Ann. **279**, 239). 5-**Phenyl**-3-**pyrazolecarboxylic acid**, m.p. 234°, from phenylacetylene and diazoacetic ester (*Buchner*, *Lehmann*, Ber. **35**, 35), and from benzoylpyruvic acid and hydrazine (*Bülow*, Ber. **37**, 2198). 3- and 4-**Phenylpyrazoledicarboxylic acid**, $C_3(C_6H_5)HN_2(COOH)_2$, m.p. 235° and 243°, are prepared from diazoacetic ester with phenylpropiolic acid and with α-bromocinnamic acid (*Buchner*, Ber. **27**, 3247; *cf.* *Buchner*, *v. der Heide*, Ber. **35**, 33). 1-**Methyl**-5-**phenylpyrazole**-3-**carboxylic acid**, m.p. 144°, and 1-**methyl**-3-**phenylpyrazole**-5-**carboxylic acid**, m.p. 183° (*v. Auwers*, *Mausolf*, Ber. **60**, 1730); the corresponding 1-ethylcarboxylic acids, m.p. 138° and 163° (*loc. cit.*). 1-**Phenylpyrazolecarboxylic acids**, $C_3H_2N_2(C_6H_5)COOH$: 3-acid, m.p. 146°, and 5-acid, m.p. 183° (*Claisen*, *Roosen*, Ber. **24**, 1888); 4-acid, m.p. 220°, from 1-phenylpyrazoletricarboxylic acid (*Knorr*, *Laubmann*, Ber. **22**, 179). Its ethyl ester, m.p. 97°, is obtained from the addition product of phenylhydrazine with formylglutaconic acid ester or with malonaldehydic acid ester by distillation in a vacuum; in both cases acetic ester splits from the pyrazoline derivative formed first (*Wislicenus*, *Breit*, Ann. **356**, 35; *Wislicenus*, *Bywaters*, Ann. **356**, 45). Five isomeric 1-**phenylmethylpyrazolecarboxylic acids** are known: the 1,5,3-acid, m.p. 136°, is prepared from acetonylacetoacetic ester with benzenediazonium chloride (p. 99, method *2*), and from ethyl acetonyl oxalate with phenylhydrazine, together with the 1,3,5-acid, melting at 190°, which is also obtained by a peculiar rearrangement of phenylmethylhydroxypyridazone (*Ach*, Ann. **253**, 54; *Claisen*, Ann. **295**, 305); the 1,5,4-acid, m.p. 166°, is prepared from hydroxymethyleneacetoacetic ester (*Claisen*, Ann. **278**, 270; **295**, 311); the 1,4,3-acid, m.p. 134°, and the 1,3,4-acid, m.p. 192°, are prepared by oxidation of phenyldimethylpyrazole (*Balbiano*, *Severini*, Atti accad.Lincei **1892**, II, 195; **1893**, I, 3). 1,5-**Diphenyl**-3-**pyrazolecarboxylic acid**, m.p. 185°, from phenacylacetoacetic ester. 1-**Phenyl**-3,4,5-**pyrazoletricarboxylic acid**, m.p. 184° (*Knorr*, *Laubmann*, Ber. **22**, 172). 1,3-**Diphenyl**-5-**methyl**-4-**pyrazolecarboxylic acid**, m.p. 194°, is obtained in the form of its ethyl ester by heating the phenylhydrazone of benzaldehyde with acetoacetic ester and $ZnCl_2$ at 130° (*Minunni*, Atti accad.Lincei [5] **14** (1906), II, 414). **1,3,5-Triphenyl-4-pyrazolecarboxylic acid,** similarly with benzoylacetic ester (*Minunni, d'Urso*, Gazz. **58,** 691).

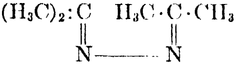
PYRAZOLINES. When reduced with sodium and alcohol, the pyrazoles, especially the N-phenylpyrazoles, are converted to dihydropyrazoles, or pyrazolines. Pyrazolines are also formed by the rearrangement of the hydrazones of α-olefincarboxaldehydes or ketones in boiling glacial acetic acid (*Auwers, Müller*, Ber. **41,** 4230; *Auwers, Voss*, Ber. **42,** 4411):



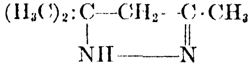
Phenylhydrazone of acrolein

1-Phenylpyrazoline

By a similar rearrangement the ketazine of acetone, bis-(dimethylmethylene)-hydrazine, is converted by maleic acid, or by other acids in the absence of water, into trimethylpyrazoline (*Frey, Hofmann*, Mo. **22,** 760):



Bis-(dimethylmethylene)-hydrazine

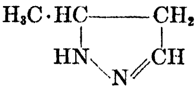


3,5,5-Trimethyl-2-pyrazoline

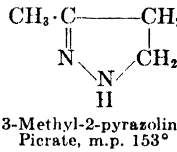
Homologous ketazines and ethylidenealdazine give other pyrazoline derivatives; isobutyraldazine is rearranged by concentrated hydrochloric acid to 4,4-dimethyl-5-isopropylpyrazoline (*Curtius, Zinkeisen*, J.pr. **58,** 910; *Franke*, Mo. **20,** 847). Some semicarbazones isomerize to pyrazolines (*Heilmann*, Bull. [4] **45,** 545). See, however, the rearrangement of bis-(diethylmethylene)-hydrazine to dimethyldiethylpyrrole when heated with $ZnCl_2$, p. 32 and *Piloty*, Ber. **43,** 493.

Behavior.—The pyrazolines are weak bases which are usually soluble only in concentrated acids. They are less stable than the pyrazoles. Oxidizing agents convert them to very unstable dyestuffs, which are derivatives of bipyrazolines (Knorr's pyrazoline reaction; *Knorr*, Ber. **26,** 100). The products of their reduction, particularly of the reduction of N-phenylpyrazolines, are principally derivatives of trimethylenediamine. Some pyrazolines can be converted to cyclopropane derivatives by loss of nitrogen [*Kischner*, J.Russ.Phys.-Chem.Soc. **45** (1913), 987]. This reaction generally takes place with pyrazolinecarboxylic acids (p. 102).

Isomerism of the Pyrazolines.—It has been noted (p. 93) that the great mobility of the hydrogen atom attached to the nitrogen atom in the pyrazole ring makes impossible the isolation of isomeric 3- and 5-alkylpyrazoles. In the pyrazoline series the situation is different; both a 3- and a 5-methylpyrazoline can be obtained (*Freudenberg, Stoll*, Ann. **440,** 38):



5-Methyl-2-pyrazoline
Picrate, m.p. 126°



3-Methyl-2-pyrazoline
Picrate, m.p. 153°

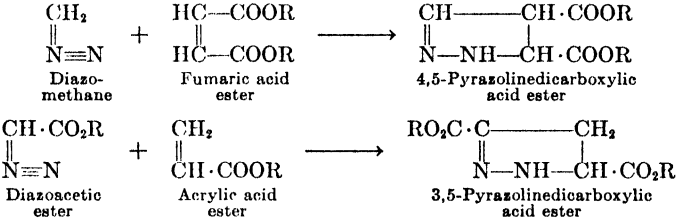
Of the corresponding phenyl derivatives, the 3-phenyl compound is the more stable one, and the 5-phenyl compound isomerizes to it very readily (*v. Auwers, Heimke*, Ann. **458,** 190). The spectrochemical data are of assistance in determining which isomer is present, since 3-phenylpyrazolines always exhibit a strong exaltation, while 5-phenylpyrazolines are optically normal (*loc. cit.*, p. 102).

For the physical properties (b.p., m.p., d, n_{He}) of 34 pyrazolines in tabular form, see *v. Auwers, Heimke*, Ann. **458,** 180.

2-Pyrazoline, $\dot{C}H_2\cdot CH_2\cdot CH:N\cdot \dot{N}H$, oil, b.p. 144°, from acrolein and hydrazine hydrate (*Wolff*, Ber. **28**, 69; *Curtius*, Ber. **29**, 774), and from ethylene and diazomethane (*Azzarello*, Atti accad.Lincei [5] **14** (1905), II, 285). **5-Methylpyrazoline**, b.p. 50° (16 mm.), picrate m.p. 126°, from crotonaldehyde and hydrazine. 3-**Methylpyrazoline**, b.p. 59° (19 mm.), picrate m.p. 153°, from β-chloroethyl methyl ketone (*Freudenberg*, *Stoll*, Ann. **440**, 38). 3,5,5-**Trimethylpyrazoline**, b.p. 66–69° (20 mm.), from mesityl oxide and hydrazine, and from bis-(dimethylmethylene)-hydrazine (page 101) (*Curtius*, *Försterling*, Ber. **27**, 770). 5-**Methyl**-3,5-**diethylpyrazoline**, b.p. 79° (14 mm.), 5-**methyl**-3,5-**dipropylpyrazoline**, b.p. 102° (14 mm.), from bis-(methylethylmethylene)- and bis-(methylpropylmethylene)-hydrazine. 4-**Phenylpyrazoline**, by addition of diazomethane to styrene (*Oliveri-Mandalà*, Gazz. **40**, I, 117), and from 4-phen pyrazoline-3,5-dicarboxylic acid (*Buchner*, *Perkel*, Ber. **36**, 3777). 3-**Phenylpyrazoline**, m.p. 45°, b.p. 165° (17 mm.) (*v. Auwers*, *Heimke*, Ann. **458**, 189). 5-**Phenylpyrazoline**, b.p. 144° (13 mm.), from the hydrazone of cinnamaldehyde (*loc. cit.*, p. 190), and from its dicarboxylic acid (*Bischoff*, *Walden*, Ber. **26**, 261). 1-**Phenylpyrazoline**, m.p. 52°, b.p. 274°, is converted by bromine to 1-phenyldibromopyrazoline, m.p. 39°. 1,5-**Diphenylpyrazoline**, m.p. 138°, from the phenylhydrazone of cinnamaldehyde. 1,3,5-**Triphenylpyrazoline**, m.p. 135°, is converted by bromine to triphenyltribromopyrazoline, m.p. 179°. 1-**Phenyl**-3,4,4-**trimethyl**-5-**hydroxypyrazoline**, $C_6H_5\overline{N\cdot N:C(CH_3)\cdot C(CH_3)_2\cdot C}H(OH)$, m.p. 118°, from the corresponding pyrazolone by reduction, is rearranged by sulfuric acid, with loss of water, to 1-phenyl-3,4,5-trimethylpyrazole (*Knorr*, *Jochheim*, Ber. **36**, 1275).

Pyrazoline ketones are formed by addition of diazomethane to α,β-unsaturated ketones, *e.g.*, 4-**phenyl**-5-**acetylpyrazoline**, $C_3H_3(C_6H_5)N_2\cdot COCH_3$, m.p. 106°, from benzylideneacetone (*Azzarello*, Gazz. **36**, II, 50).

Pyrazolinecarboxylic acids are prepared from diazoacetic ester and olefin mono- and dicarboxylic acids or monohalogenated saturated acids (*cf.* p. 98); diazomethane reacts similarly. Identical products are obtained from maleic and fumaric acid, from citraconic and mesaconic acid and from crotonic and isocrotonic acid (*Pechmann*, *Burkard*, Ber. **33**, 3590):



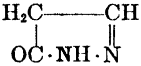
When heated alone, the pyrazolinecarboxylic acids lose nitrogen, forming cyclopropanecarboxylic acids. When heated with hydrochloric acid, they split off hydrazine. Oxidation with bromine converts them to pyrazolecarboxylic acids; heating of their silver salts gives pyrazoles. On reduction some pyrazolidine derivatives are formed (p. 111) (*Buchner*, Ann. **273**, 214; *cf. Pechmann*, *Burkard*, Ber. **33**, 3590).

2-**Pyrazoline**-3,5-**dicarboxylic acid**, m.p. 242° (dec.) (*Buchner*, Ann. **273**, 214). **Pyrazoline**-4,5-**dicarboxylic acid methyl ester** (see above) (*v. Pechmann*, Ber. **27**, 1890). **Pyrazoline**-3,4,5-**tricarboxylic acid methyl ester**, $C_3H_3N_2(COOCH_3)_3$, m.p. 61°, from diazoacetic ester with fumaric acid ester. 5-**Carbomethoxymethylpyrazoline**-3,4,5-**tricarboxylic acid methyl ester**, $C_3H_2N_2(COOCH_3)_3$-(CH_2COOCH_3), m.p. 105°, from diazoacetic ester with aconitic acid ester, and from diazosuccinic acid ester with fumaric acid ester. Pyrazolinetricarboxylic acid ester is also formed by heating diazoacetic ester alone, and carbomethoxymethylpyrazolinetricarboxylic acid ester by heating diazosuccinic acid ester alone; in both cases the diazo compound partially decomposes to fumaric acid ester, which then condenses with the diazo ester (*Buchner*, *v. der Heide*, Ber. **34**, 345; *Darapsky*, Ber. **43**, 1095; **46**, 863). 4-**Phenylpyrazoline**-3,5-**dicarboxylic acid** ester is obtained in two isomeric forms, m.p. 76° and 107°, from the ethyl ester of cinnamic acid and the methyl ester of diazoacetic acid, and from the methyl ester of the former and the ethyl ester of the latter, the isomerism disappearing on oxidation to the pyrazole derivatives (*Buchner, v. der Heide*, Ber. **35**, 31). **4-Phenyl-5-acetylpyrazoline-3,5-dicarboxylic acid ester**, from cinnamoylacetic ester and diazoacetic ester, does not form a cyclopropane derivative on heating, but a 1,2-pyrone derivative (*Buchner, Schröder*, Ber. **35**, 782).

PYRAZOLONES

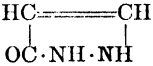
Pyrazolones, which are the most important class of pyrazole derivatives, are derived from pyrazolines, by replacement of a methylene group by a CO-group. In this group are included two isomeric pyrazolones, *5-oxo-2-pyrazoline* or *5-pyrazolone*, and *3-oxo-4-pyrazoline* or *3-pyrazolone*. 4-Oxo-2-pyrazoline reacts almost exclusively in the tautomeric form as 4-pyrazolol, and has been described on p. 98.

(I)



$$\begin{array}{lcl} H_2C & \text{—} & CH \\ | & & \| \\ OC & \cdot NH \cdot & N \end{array}$$

5-Pyrazolone

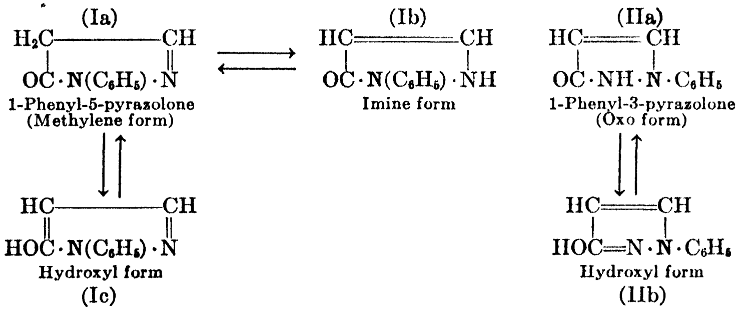


$$\begin{array}{lcl} HC & = & CH \\ | & & | \\ OC & \cdot NH \cdot & NH \end{array}$$

(II)

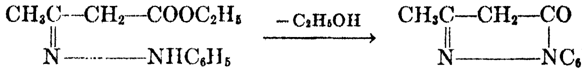
3-Pyrazolone

These two possible isomers cannot be isolated when the pyrazolone is unsubstituted, presumably because the mobility of the hydrogen atom in the imine or in the methylene group makes Formulas I and II tautomeric. However, two totally different N-phenylpyrazolones are known: 1-phenyl-5-pyrazolone, p. 104, and 1-phenyl-3-pyrazolone, p. 108:



The oxo form (Ia and IIa) is the predominating one for the pyrazolones, but with many reagents (especially alkylating and acylating agents) 1-alkyl- or 1-aryl-5-pyrazolones react in the tautomeric imine form (Ib). The existence of the hydroxyl forms (Ic and IIb) has been discussed on p. 97. The pyrazolones were discovered by *Knorr* in 1883. Various pyrazolones have already been described in connection with the hydrazones of β-oxo carboxylic acids, since they are the inner anhydrides of such hydrazones, as lactams are the inner anhydrides of the corresponding aminocarboxylic acids.

5-PYRAZOLONES. This most important group of pyrazolones is prepared: (*1*) By elimination of alcohol from the hydrazones of β-oxo carboxylic acids:



$$\begin{array}{l} CH_3C{-}CH_2{-}COOC_2H_5 \\ \| \\ N{-}{-}{-}{-}NHC_6H_5 \end{array} \xrightarrow{-C_2H_5OH} \begin{array}{l} CH_3C{-}CH_2{-}CO \\ \| \qquad\qquad | \\ N{-}{-}{-}{-}NC_6H_5 \end{array}$$

Phenylhydrazone of acetoacetic ester — 1-Phenyl-3-methyl-5-pyrazolone

Condensing agents which remove water, such as hydrochloric acid and acetyl chloride, convert a number of these hydrazones to *alkoxypyrazoles* (p. 98), which yield pyrazolones when the alkoxy group is saponified [*cf. De*, Quart.J.Indian Chem.Soc. **3** (9126), 30]. Some phenylhydrazones of β-oxocarboxylic acid esters form *indole* derivatives (p. 63) under the influence of concentrated sulfuric acid.

5-Pyrazolones are formed similarly from several other derivatives of hydrazine, such as semicarbazides and thiosemicarbazides [*De*, Quart.J.Indian Chem.Soc. **3** (1926), 30; *De, Dutt, ibid.*, **5** (1928), 459].

(*2*) From acetylenecarboxylic acid esters and hydrazines (*Rothenburg*, Ber. **27**, 783; *Moureu, Lazennec*, C.r. **142**, 1534).

(*3*) By oxidation of the corresponding pyrazolidones.

Behavior.—The pyrazolones form unstable salts with bases as well as with acids, being weak bases like the other pyrazoles, but having also the acid properties of β-oxocarboxylic acid esters. They also resemble β-oxocarboxylic acid derivatives in the behavior of the methylene group between the CO- and the CN-groups toward a number of reagents: With benzaldehyde they condense to *benzylidene* compounds, with nitrous acid they form yellowish red *isonitroso* derivatives, and with benzenediazonium salts they couple to give more or less strongly colored *azo* compounds (*cf. Rothenburg*, Ber. **27**, 782; *Stolz*, Ber. **28**, 625). With $POCl_3$ the pyrazolones give chlorinated pyrazoles (p. 96), with phosphorus tribromide under pressure they give pyrazoles directly (*Stoermer, Martinsen*, Ann. **352**, 332). Heating with P_2S_5 in xylene solution converts pyrazolones to *thiopyrazolones*, while heating without a solvent to a higher temperature results in the formation of pyrazoles (*cf.* p. 93 and *Stoermer, Johannsen*, Ber. **40**, 3701; *Michaelis*, Ann. **361**, 251). The alkylation of pyrazolones is complicated, since alkylation products of all the tautomeric forms can be obtained (see p. 103, formulas Ia,b,c). The course of the reaction is greatly influenced by the method used (see antipyrine). Acylation also leads to the formation of several different products (*Stolz*, J.pr. **55**, 145, 154).

5-Pyrazolone, $\overline{CO\cdot CH_2\cdot CH{:}N\cdot NH}$, m.p. 164°, is most advantageously prepared from malonaldehydic acid ester with hydrazine; it is also formed from its carboxylic acid (page 109). With benzaldehyde it gives **4-benzylidene-5-pyrazolone**, $(C_3H_2ON_2){:}CHC_6H_5$, m.p. 200°, and with nitrous acid, **4-isonitroso-5-pyrazolone**, $(C_3H_2ON_2){:}NOH$, m.p. 181° (dec.). It couples with benzenediazonium chloride, forming **4-benzeneazo-5-hydroxypyrazole**, $(C_3H_3ON_2)\cdot N{:}NC_6H_5$ (*Knorr*, Ber. **29**, 249).

3-Methyl-5-pyrazolone, m.p. 215°, is obtained from acetoacetic ester or dehydroacetic acid and hydrazine (*Abenius*, J.pr. **39**, 132); when heated with dry sodium alcoholate it forms 3-methyl-4-alkylpyrazoles (*Wolff, Thielepape*, Ann. **420**, 275). **3-Phenyl-5-pyrazolone**, $C_3(C_6H_5)H_3ON_2$, m.p. 236°, from benzoylacetic ester and hydrazine (*Michaelis*, Ann. **352**, 158). **1-Phenyl-5-pyrazolone**, m.p. 118°, is prepared from the corresponding 3- and 4-carboxylic acids or from 1-phenyl-5-pyrazolidone (*Claisen, Haase*, Ber. **28**, 35; *Stolz*, Ber. **28**, 630).

1-Phenyl-3-methyl-5-pyrazolone, $\overline{CO\cdot CH_2\cdot C(CH_3){:}N\cdot NC_6H_5}$, m.p. 127°, from acetoacetic ester, β-chlorocrotonic acid ester (*Autenrieth*, Ber. **29**, 1654) or tetrolic acid (Vol. I) with phenylhydrazine, was the first pyrazolone derivative to be discovered, and is now the best known, being prepared technically on a large scale (*Knorr*, Ann. **238**, 147). Its cobalt and silver salts are particularly characteristic. With benzaldehyde it gives the benzylidene compound,

$$\overline{CO\cdot C({:}CHC_6H_5)\cdot C(CH_3){:}N\cdot NC_6H_5}$$

m.p. 107°; the condensation product with hydroxybenzaldehyde is highly colored (*Tambor*, Ber. **33**, 864). When 1-phenyl-3-methyl-5-pyrazolone is heated in alcoholic solution in the presence of piperidine for a long time, di- and trimolecular condensation products are formed (*Jonescu, Georgescu*, Bull. [IV] **41**, 1514). It reacts with $POCl_3$ to give 1-phenyl-3-methyl-5-chloropyrazole (p. 96), and with P_2S_5 in xylene to give **1-phenyl-3-methyl-5-thiopyrazolone**,

$$\mathrm{CS\cdot CH_2C(CH_3):N\cdot NC_6H_5},$$

m.p. 109° (*Pander*, Ann. **361**, 261).

Nitric acid attacks the benzene ring as well as the pyrazole ring (4-position). **Picrolonic acid**, 1-(*p-nitrophenyl*)*-3-methyl-4-nitro-5-pyrazolone*, m.p. 116.5°, is formed (*Knorr*, Ber. **30**, 914; preparation: *Hugounenq, Florence, Couture*, Bull. [IV] **7**, 58). It is often used in place of picric acid for the isolation of bases containing nitrogen.

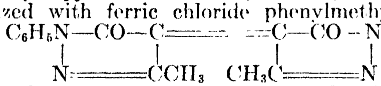
With N_2O_3 phenylmethylpyrazolone gives an isonitroso compound,

$$\mathrm{CO\cdot C(NOH)\cdot C(CH_3):N\cdot NC_6H_5},$$

m.p. 157°, which can be oxidized to the **4-nitro**-derivative, m.p. 127°, and reduced to **4-amino-1-phenyl-3-methyl-5-pyrazolone**. The latter is also obtained by reduction of 1-phenyl-3-methyl-4-benzeneazo-5-hydroxypyrazole (constitution: *v. Auwers*, Ann. **378**, 218), which is prepared from phenylmethylpyrazolone and benzenediazonium chloride. The aminophenylmethylpyrazolone is not stable, being oxidized by the air to rubazonic acid,

$$\mathrm{C\cdot (CH_3):N\cdot N(C_6H_5)\cdot CO\cdot CH\cdot N:C\cdot CO\cdot N(C_6H_5)\cdot N:C(CH_3)},$$

m.p. 181°, a red compound which corresponds in behavior to purpuric acid of the uric acid group. It can also be obtained from aminopyrazolone (see above) and from the 4-hydroxyphenylmethylpyrazolone mentioned below. With a large excess of oxidizing agent the aminopyrazolone is converted immediately to **1-phenyl-3-methyl-4,5-pyrazoledione**, $\mathrm{CO\cdot CO\cdot C(CH_3):N\cdot NC_6H_5}$, bronze crystals, m.p. 119°, the isatin of the pyrazole group, which is also prepared by fission of its 4-dimethylamino anil, the condensation product of nitrosodimethylaniline and phenylmethylpyrazolone. On reduction this pyrazoledione forms **1-phenyl-3-methyl-4-hydroxy-5-pyrazolone** (*Knorr, Pschorr*, Ann. **293**, 50).

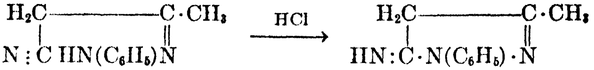
When oxidized with ferric chloride phenylmethylpyrazolone condenses to pyrazole blue, 

$$\begin{array}{cccc} \mathrm{C_6H_5N{-}CO{-}C} & \mathrm{=\!=} & \mathrm{=\!=C{-}CO{-}NC_6H_5} & \\ | \qquad\quad | & & | \qquad\quad | & \\ \mathrm{N{=\!=\!=}CCH_3} & & \mathrm{CH_3C{=\!=\!=}N} & \end{array}$$

, which is analogous in constitution and behavior to indigo (p. 78), and which is also known as 4,4′*-di-*(1*-phenyl-3-methylpyrazole*)*-indigo*. Milder oxidizing agents, such as phenylhydrazine, give the dihydro derivative of this compound, bi-4,4′-(1-phenyl-3-methyl-5-pyrazolone) (*Michaelis, Rademacher, Schmiedekampf*, Ann. **354**, 55), which is also obtained from the silver salt of phenylmethylpyrazolone with iodine. Phenylmethylpyrazolone when treated with diazomethane yields phenylmethylmethoxypyrazole (p. 98), and a small quantity of the isomeric antipyrine (*cf. v. Pechmann*, Ber. **28**, 1626).

1-Phenyl-4-methyl-5-pyrazolone, $\mathrm{C_6H_5N\cdot N:CH\cdot CH(CH_3)\cdot CO}$, m.p. 148°, from β-formylpropionic acid ester and phenylhydrazine, and from bromomethacrylic acid ester, $\mathrm{CHBr:C(CH_3)\cdot COOR}$, and phenylhydrazine, together with some 1-phenyl-4-methyl-3-pyrazolone (p. 109) (*Stolz*, Ber. **38**, 3273). **1-Methyl-3-phenyl-5-pyrazolone**, $\mathrm{CH_3N\cdot N:C(C_6H_5)\cdot CH_2\cdot CO}$, m.p. 207°, by methylation of 3-phenyl-5-pyrazolone (p. 104) and by condensation of benzoylacetic ester with methylhydrazine; it is completely analogous in its reactions to 1-phenyl-3-methyl-5-pyrazolone (*Michaelis*, Ann. **352**, 152). **1,3-Diphenyl-5-pyrazolone**, $\mathrm{C_6H_5N\cdot N:C(C_6H_5)\cdot CH_2\cdot CO}$, m.p. 137°, from benzoylacetic ester and phenylhydrazine (*Michaelis, Willert*, Ann. **358**, 171), can be converted, similarly to phenylmethylpyrazolone, to **1,3-diphenyl-4,5-pyrazoledione** and **4-hydroxy-1,3-diphenyl-5-pyrazolone** (*Sachs, Becherescu*, Ber. **36**, 1132).

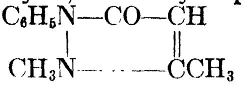
5-Iminopyrazolines, *5-pyrazoloneimines*, have been prepared from β-oxo carboxylic acid nitriles or nitriles of acetylenecarboxylic acids with hydrazine or arylhydrazines. The hydrazones or arylhydrazones which are formed first isomerize under the influence of hydrochloric acid to iminopyrazolones:



$$\begin{array}{l} H_2C\text{———}C\cdot CH_3 \\ N:C\;HN(C_6H_5)N \end{array} \xrightarrow{HCl} \begin{array}{l} H_2C\text{———}C\cdot CH_3 \\ HN:C\cdot N(C_6H_5)\cdot N \end{array}$$

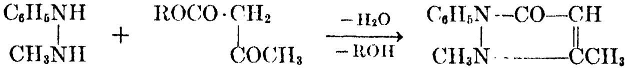
Pyrazolone-3(5)-imine, b.p. 282°, from pyrazole-3(5)-carboxylic acid azide. **1-Phenyl-3-methyl-5-pyrazoloneimine,** m.p. 116° (see iminopyrines, p. 107). The iminopyrazolines are tautomeric with the aminopyrazoles.

ANTIPYRINE, 1-phenyl-2,3-dimethyl-5-pyrazolone,



$$\begin{array}{l} C_6H_5N\text{—}CO\text{—}CH \\ CH_3N\text{———}CCH_3 \end{array}$$

m.p. 112°, distillable under reduced pressure, is obtained in the form of its hydriodide by the reaction of phenylmethylpyrazolone with methyl iodide and methanol at 100°, or by heating the sodium salt of phenylmethylpyrazolone with dimethyl sulfate in aqueous methanol solution (*Grandmougin et al.*, Chem.-Ztg. **37,** 813). It is also formed by the condensation of *s*-phenylmethylhydrazine with acetoacetic ester (*Knorr,* Ann. **238,** 160; Ger. Pat. 40377, 1886):



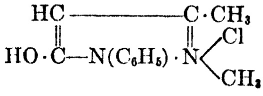
$$\begin{array}{l} C_6H_5NH \\ CH_3NH \end{array} + \begin{array}{l} ROCO\cdot CH_2 \\ \quad COCH_3 \end{array} \xrightarrow[-ROH]{-H_2O} \begin{array}{l} C_6H_5N\text{—}CO\text{—}CH \\ CH_3N\text{———}CCH_3 \end{array}$$

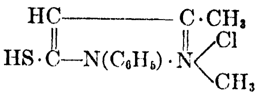
The crude antipyrine is best purified by conversion to the sparingly soluble perchlorate (Ger. Pat. 417696, 1921).

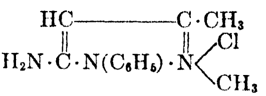
Antipyrine is a very strong monoacid base (hydrochloride, m.p. 158–160°), readily soluble in water and alcohol, and crystallizing from ether or toluene in shiny platelets. In medicine it is highly esteemed as an antipyretic; its salicylate, **salipyrine** (m.p. 92°), and *p*-tolyldimethylpyrazolone, **tolypyrine,** as well as other homologues, have a similar action. For molecular compounds of antipyrine with phenols, see *Bodforss, Guthe,* Ber. **57,** 842. Antipyrine can be catalytically hydrogenated to *dihydroantipyrine* (m.p. 105°) (*Waser,* Helv. **8,** 117).

Other 1-phenyl-2-alkyl-5-pyrazolones can be prepared in a similar manner from phenylmethylpyrazolone by alkylating agents: **2-benzyl-** and **2-ethyl-1-phenyl-3-methyl-5-pyrazolone,** m.p. 119° and 73°, respectively. Antipyrine and its homologues are also formed by heating the alkyl halide addition products of 5-alkoxypyrazoles (p. 98) or 5-chloropyrazoles (p. 96) with aqueous alkali; the methyl iodide of 1-phenyl-5-chloropyrazole with alkali gives **1-phenyl-2-methyl-5-pyrazolone,** m.p. 117°, which is also obtained from 1-phenyl-5-pyrazolone with methyl iodide (*Michaelis,* Ann. **320,** 28). The isomers of antipyrine, **1,2-dimethyl-3-phenyl-5-pyrazolone,** m.p. 108°, and **1-phenyl-2,4-dimethyl-5-pyrazolone,** m.p. 125°, are prepared by methylation of 1-methyl-3-phenyl- and 1-phenyl-4-methyl-5-pyrazolone (*Michaelis, Dorn,* Ann. **352,** 175; *Stolz,* Ber. **38,** 3275). For **1,2,3-trimethyl-5-pyrazolone,** see *Michaelis, Lachwitz,* Ber. **43,** 2106.

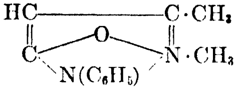
Reactions of the Antipyrines.—Antipyrine (and also its homologues) is converted by $POCl_3$ to **antipyrine chloride,** the 2-methyl chloride addition product of *1-phenyl-3-methyl-5-chloropyrazole,* m.p. 137°; the chlorine atoms, especially the one in the 5-position, are very easily replaced. Alkali regenerates antipyrine, alkali hydrosulfides or sodium thiosulfate give thiopyrine (page **107**), and ammonia and amines give iminopyrine. These compounds are strong bases like antipyrine itself and, in contrast to other pyrazole and pyrazolone derivatives, form stable salts with acids. The salts are quaternary ammonium salts, corresponding to the formulas:



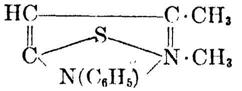




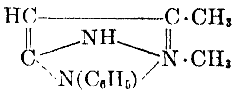
They are alkyl halide addition products of 5-hydroxy-, 5-mercapto- and 5-aminopyrazoles. The salts are derived from their bases by an addition of acid in the 2,5-position of the pyrazole ring; *Michaelis* has proposed these structures for the free bases (*Michaelis*, Ann. **320**, 1; **331**, 197; **339**, 117; *Michaelis*, *Hepner*, Ber. **36**, 3271; *Knorr*, Ann. **328**, 78):



Antipyrine



Thiopyrine



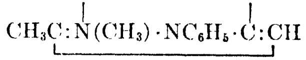
Iminopyrine

The compound obtained from antipyrine chloride with *p*-toluidine differs from that from tolypyrine chloride with aniline (*Michaelis*, Ann. **339**, 130; **352**, 154). This fact does not invalidate the "betaine formula" of *Michaelis*, since the fourth and fifth valences of nitrogen are known to be different.

All 1,2-dialkylpyrazolones behave like antipyrine and its homologues (*cf.* *Michaelis*, *Dorn*, Ann. **352**, 175; *Michaelis*, *Rademacher*, *Schmiedekampf*, Ann. **354**, 55; *Michaelis*, *Lachwitz*, Ber. **43**, 2106).

THIOPYRINES. **1-Phenyl-2-methylthiopyrazole**, m.p. 162°, from the 2-methyl iodide of 1-phenyl-5-chloropyrazole with KSH. **1-Phenyl-2,3-dimethylthiopyrazole**, *thiopyrine*, m.p. 166°, from antipyrine chloride with KSH or $Na_2S_2O_3$ in aqueous solution, has an antipyretic action like antipyrine. **1-Phenyl-2-ethylthiopyrazole**, m.p. 171°; **1-phenyl-2,3,4-trimethylthiopyrazole**, m.p. 129°. By repeated distillation, or by heating their alkyl halide addition products, thiopyrines are converted by a shift of the alkyl group from N to S to pseudothiopyrines or alkylthiopyrazoles such as $CH_3{\cdot}C{:}N{\cdot}N(C_6H_5){\cdot}C(SCH_3){:}CH$. Thiopyrines and pseudothiopyrines behave differently when oxidized: the former give trioxides, *inner salts of sulfonic acids*, such as $CH_3C{:}N(CH_3){\cdot}NC_6H_5{\cdot}C{:}CH$ while the latter give dioxides, *sulfones*, such as

$$CH_3C{:}N{\cdot}N(C_6H_5){\cdot}C(SO_2CH_3){:}CH$$



$$\overset{O\text{———————}SO_2}{CH_3C{:}N(CH_3){\cdot}NC_6H_5{\cdot}C{:}CH}$$

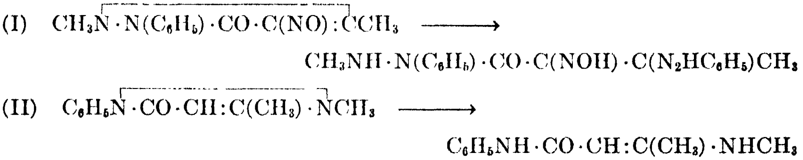
IMINOPYRINES. **1-Phenyl-2,3-dimethyliminopyrazole**, *iminopyrine* (formula given above), m.p. 63°, from antipyrine chloride by heating with aqueous ammonia or ammonium carbonate under pressure; its hydrochloride decomposes when heated into CH_3Cl and 1-phenyl-3-methyl-5-aminopyrazole, which can be reconverted to the iminopyrine hydriodide by addition of methyl iodide. **Anilinopyrine**, m.p. 59°, from antipyrine chloride and aniline, is transformed by heating its methyl iodide to **1-phenyl-3-methyl-5-methylanilinopyrazole**. For **phenylhydrazinopyrine**, see *Michaelis*, *Kobert*, Ber. **42**, 2765. For other iminopyrines, see *Stolz*, Ber. **36**, 3279. For hydrazinopyrines, see *Thielepape*, *Spreckelsen*, Ber. **55**, 2936.

Like acids, alkyl iodides add in the 2,5-position of antipyrine, forming methyl iodides of 5-alkoxypyrazoles (p. 98); at higher temperatures antipyrine and methyl iodide give **1-phenyl-2,3,4-trimethyl-5-pyrazolone**, *methylantipyrine*, m.p. 82°, and also, by rearrangement, **1-phenyl-3,3,4-trimethyl-5-pyrazolone**, m.p. 56° (*Knorr*, Ann. **293**, 1).

4-Nitrosoantipyrine, which detonates when heated, is prepared from antipyrine with nitrous acid; when reduced with zinc and acetic acid it gives **4-aminoantipyrine**, m.p. 109°, from whose diazo derivative dyes are obtained (*Knorr*, *Stolz*, Ann. **293**, 58). The aminoantipyrine is converted by treatment with methyl iodide, dimethyl sulfate or formaldehyde and a little formic acid (Ger. Pat. 360423, 1918; Brit. Pats. 214261, 223192, 1923) into **pyramidone**, *4-dimethylamino-2,3-dimethyl-1-phenyl-5-pyrazolone*, m.p. 108° (Ger. Pats. 90959, 1896; 111724, 1899), which is transformed by the human body largely to antipyrylurea and rubazonic acid (see p. 110) (*Jaffe*, Ber. **35**, 2891). Pyramidone, by itself an important antipyretic, is also a constituent of numerous other pharmaceuticals: *Trigemin* (pyr. + butylchloral hydrate: *Pfeiffer, Seydel*, Z.physiol.Chem. **178**, 97); *Veramon* (2 pyr. + 1 barbital: *Pfeiffer, Seydel*, Z.physiol.Chem. **176**, 1); *Compral* (1 pyr. + 1 voluntal: *Pfeiffer, Seydel*, Z. physiol.Chem. **178**, 81); *Perdolat* (pyr. + cinchophen + caffeine); *Allional* [addition product of pyr. with isopropyl-propenylbarbituric acid: *Mentzel*, Pharm.Zentralhalle **65** (1924), 535]; *Cibalgin* [pyr. + diallylbarbituric acid: *Auer*, München. med.Wochschr. **73** (1926), 24].

4-Hydroxyantipyrine, m.p. 182°, is formed by methylation of 4-hydroxy-1-phenyl-3-methylpyrazolone (p. 105); it has marked phenolic properties (*Knorr, Pschorr*, Ann. **293**, 49).

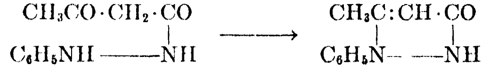
Disintegration Products.—When heated with alcoholic KOH at 130° antipyrine is split, forming *phenylmethylhydrazine* (p. 96 and *Knorr*, Ber. **39**, 3265). When nitrosoantipyrine (I) is heated with phenylhydrazine, the *phenylhydrazone of isonitrosoacetoacetic acid phenylmethylhydrazide* is produced (*Knorr*, Ann. **328**, 62). When antipyrine (II) is heated with toluene and sodium in an atmosphere of CO_2, *β-methylaminocrotonanilide* is obtained (*Knorr, Taufkirch*, Ber. **25**, 769):



$$\text{(I)}\quad CH_3N\cdot N(C_6H_5)\cdot CO\cdot C(NO){:}CCH_3 \longrightarrow CH_3NH\cdot N(C_6H_5)\cdot CO\cdot C(NOH)\cdot C(N_2HC_6H_5)CH_3$$

$$\text{(II)}\quad C_6H_5N\cdot CO\cdot CH{:}C(CH_3)\cdot NCH_3 \longrightarrow C_6H_5NH\cdot CO\cdot CH{:}C(CH_3)\cdot NHCH_3$$

3-PYRAZOLONES (*cf.* p. 97) are prepared: (*1*) By the action of PCl_3 on a mixture of β-oxocarboxylic acid esters and acetyl- or benzoylphenylhydrazine; phenylhydrazides of β-oxocarboxylic acids are probably formed first (*Michaelis*, Ann. **338**, 269):



$$\begin{matrix} CH_3CO\cdot CH_2\cdot CO \\ C_6H_5NH\text{———}NH \end{matrix} \longrightarrow \begin{matrix} CH_3C{:}CH\cdot CO \\ C_6H_5N\text{— —}NH \end{matrix}$$

(*2*) By the action of phenylhydrazine on β-hydroxyalkylacrylic acid ester (*Conrad, Zart*, Ber. **39**, 2282).

(*3*) By oxidation of the corresponding 3-pyrazolidones.

Behavior.—The 3-pyrazolones resemble the 5-pyrazolones in behavior; like the latter, they have both acidic and basic properties. $POCl_3$ converts them to 3-chloropyrazoles; with benzenediazonium salts they form azo dyes (*Michaelis*, Ann. **338**, 228); with N_2O_3 they give green 4-nitroso compounds, which oxidize to strongly acid 4-nitro compounds and reduce to stable 4-aminopyrazolones resistent to oxidation. When boiled with ferric chloride they do not form compounds similar to pyrazole blue. The melting points of the 3-pyrazolones are always higher than those of the corresponding 5-pyrazolones.

1-Phenyl-3-pyrazolone, $CH{:}CH\cdot CO\cdot NH\cdot N\cdot C_6H_5$, m.p. 155°, is obtained from 1-phenyl-3-pyrazolone-4-carboxylic acid by heating, from 1-phenyl-3-pyrazolidone by oxidation with ferric chloride, and from 1-phenylpyrazoline by treatment with Br and then with aqueous KOH (*Harries, Loth*, Ber. **29**, 519; *Michaelis, Remy*, Ber. **40**, 1020). **1,5-Diphenyl-3-pyrazolone**, $C_6H_5C{:}CH\cdot CO\cdot NH\cdot NC_6H_5$, m.p. 252°, by method *1*, *2*, or *3*, or by distillation of cinnamic acid phenylhydrazide (*Knorr*, Ber. **20**, 1107; *Willert*, Ann. **358**, 159). **1-Phenyl-5-methyl-3-pyrazolone**, $CH_3C{:}CH\cdot CO\cdot NH\cdot NC_6H_5$, m.p. 167°, by method *1* or *3*; methylation converts it to the isomer of antipyrine, the *poisonous* 3-**antipyrine, 1-phenyl-2,5-dimethyl-3-pyrazolone**, $CH_3C{:}CH\cdot CO\cdot N(CH_3)NC_6H_5$, m.p. 119° (*Lederer*, J.pr. **45**, 83; *Stolz*, Ber. **28**, 629); this compound is completely analogous to antipyrine in its chemical behavior: with $POCl_3$ it forms the **methyl chloride addition product** of **1-phenyl-5-methyl-3-chloropyrazole**, analogous to antipyrine chloride, which gives **3-iminopyrine** with ammonia, **3-thiopyrine** with potassium hydrosulfide and 3-**selenopyrine** with potassium hydroselenide (*Stolz*, Ber. **36**, 3290; *Michaelis*, Ann. **338**, 290). **1-Phenyl-4-methyl-3-pyrazolone,**

$CH:C(CH_3)\cdot CO\cdot NH\cdot NC_6H_5$,

m.p. 210°, is obtained together with 1-phenyl-4-methyl-5-pyrazolone from bromomethacrylic acid ester and phenylhydrazine (*Stolz*, Ber. **38**, 3273).

1-Phenyl-3-methyl-5-pyrazolone-4-carboxaldehyde,

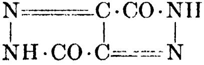
$C_6H_5\cdot N\cdot N:C(CH_3)\cdot CH(CHO)\cdot CO$,

m.p. 174°, is prepared from the condensation product of methylphenylpyrazolone with α-isatin anil by treatment with aqueous sodium hydroxide (*cf.* p. **77** and *Felix, Friedländer*, Mo. **31**, 73).

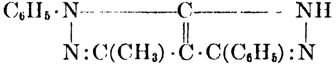
PYRAZOLONECARBOXYLIC ACIDS. The esters of these acids are obtained from the hydrazones of β-oxo or formyldicarboxylic acid esters; the acids decompose readily into CO_2 and pyrazolones.

5-Pyrazolone-3-carboxylic acid, $CO\cdot CH_2\cdot C(COOH):N\cdot NH$, dec. 250°, methyl ester, m.p. 227°, from the methyl ester of oxalacetic acid, chlorofumaric acid ester (*Ruhemann*, J. **69**, 1394) or acetylenedicarboxylic acid ester with hydrazine (*Rothenburg*, Ber. **25**, 3442; **26**, 1722); the acid yields 5-pyrazolone (p. 104) on decarboxylation, and an isonitroso compound, m.p. 201°, with nitrous acid; the latter compound is transformed to the hydrazide of hydrazipyrazolonecarboxylic acid by treatment with hydrazine hydrate. The anhydride of this acid (I), dec. 126°, has a symmetrical dicyclic nucleus, which may also be considered as a double anhydride of dioxosuccinic acid osazone (*Rothenburg*, Ber. **26**, 2057); *cf.* the diphenylmethylbipyrazole (II) obtained from 1-phenyl-3-methyl-4-benzoyl-5-chloropyrazole and hydrazine (*Michaelis, Bender*, Ber. **36**, 523), and the phenylmethylpyrazolo[4,3]pyrazolone (III) obtained from 4-dimethylaminoazoantipyrine by heating with elimination of dimethylamine (*Stolz*, Ber. **41**, 3849):

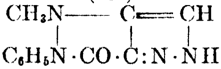
(I)



(II)



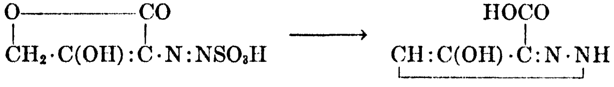
(III)



5-Pyrazolone-4-carboxylic acid, $CO—CH(COOH)—CH═N—NH$, **ethyl ester** m.p. 181°, is prepared from propylene-1,1,3,3-tetracarboxylic acid ester, $(COOR)_2CH\cdot CH:C(COOR)_2$, with hydrazine hydrate, or from ethoxymethylenemalonic acid ester with hydrazine (*Ruhemann, Orton*, J. **67**, 1002). The acid loses CO_2 readily to give 5-pyrazolone (p. 104) (*Ruhemann, Morrell*, Ber. **28**, 988).

3-Carbethoxymethyl-5-pyrazolone, $(C_2H_5OCOCH_2)C_3H_3ON_2$, m.p. 190°, from β-oxo glutaric acid ester and hydrazine (*Kufferath*, J.pr. **64**, 334).

4-Hydroxypyrazole-3-carboxylic acid, m.p. 205°, from the diazosulfonate of tetronic acid (Vol. I, p. 599) by warming with aqueous sodium hydroxide, is isomeric with the 5-pyrazolonecarboxylic acids (*Wolff, Lüttringhaus*, Ann. **313**, 6):



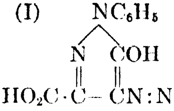
When heated it gives 4-pyrazolol (p. 98).

1-Phenyl-5-pyrazolone-4-carboxylic acid, $CO—CH(COOH)—CH═N—NC_6H_5$, m.p. 93° (dec.), ethyl ester, m.p. 118°, is prepared from propylene-1,1,3,3-tetracarboxylic acid ester with phenylhydrazine, or from ethoxymethylenemalonic acid ester with phenylhydrazine. The isomeric **1-phenyl-5-pyrazolone-3-carboxylic acid,** m.p. 181°, is obtained in the form of its ester from oxalacetic ester and phenylhydrazine. Both phenylpyrazolonecarboxylic acids give the same phenylpyrazolone (p. 104) (*Kiliani*, Ber. **28**, 41). **1-Phenyl-3-pyrazolone-4-carboxylic acid**, $\overline{CH:C(COOH)\cdot CO\cdot NH\cdot N}C_6H_5$, m.p. 216° (dec.), is obtained in the form of its ester by the action of PCl_3 on a mixture of ethoxymethylenemalonic ester and acetylphenylhydrazine (*Michaelis*, *Remy*, Ber. **40**, 1020). **1-Phenyl-4-hydroxypyrazole-3-carboxylic acid**, m.p. 154°, from the phenylhydrazone of γ-bromoacetoacetic ester, forms 1-phenyl-4-pyrazolol on decarboxylation (p. 98).

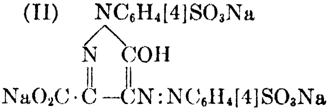
PYRAZOLONE AZO DYES. The ability of phenylmethylpyrazolones (p. 104) to couple with diazonium salts is also possessed by other 5-pyrazolones which are not substituted in the 4-position. Besides the direct preparation from pyrazolones and diazonium salts, pyrazolone azo dyes are also obtained by the reaction of hydrazines and benzeneazo β-oxo carboxylic acid esters (from β-oxo carboxylic acid esters and diazonium salts; *cf.* benzeneazoacetoacetic ester) (*Bülow*, Ber. **32**, 197). These dyes have been shown to be azo derivatives of 5-pyrazolol (*v. Auwers*, Ann. **378**, 218). Some of them have considerable commercial importance (Ger. Pats. 117575, 1900; 134162, 1900). The valuable yellow dyestuff, *tartrazine*, belongs to this group.

The ester of **1-phenyl-4-benzeneazo-5-hydroxypyrazole-3-carboxylic acid** (I), red, m.p. 154°, prepared from dioxosuccinic acid ester osazone (Vol. I), is the parent compound of tartrazine whose principal constituent is the trisodium salt of tartrazinic acid, 1-(*p*-**sulfophenyl**)-4-(*p*-**sulfobenzeneazo**)-5-**hydroxypyrazole**-3-**carboxylic acid** (II):

(I)



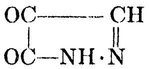
(II)



The latter acid is also obtained from 1-(*p*-**sulfophenyl**)-5-**pyrazolone**-3-**carboxylic acid** (*tartrazinogenic acid*) and diazobenzenesulfonic acid, which proves its constitution. *Aminotartrazinogenic acid* is produced by the reduction of tartrazine with zinc dust and water (*Anschütz*, Ann. **294**, 219; **306**, 1; *Gnehm*, *Benda*, Ann. **299**, 100).

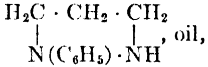
Pyrazolediones

Rubazonic acid, mentioned on p. 105, is a derivative of 4,5-pyrazoledione,



Pyrazolidines

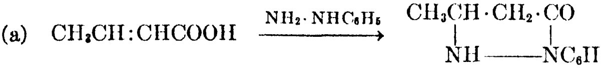
The derivatives of tetrahydropyrazole, the pyrazolidines, generally pass readily into pyrazoline derivatives, and therefore have reducing properties. The simplest pyrazolidine is not known.

N-Phenylpyrazolidine,  $\begin{array}{l} H_2C\cdot CH_2\cdot CH_2 \\ \vert \qquad\qquad\quad \vert \\ N(C_6H_5)\cdot NH \end{array}$, oil, b.p. 160° (20 mm.), is obtained from trimethylene dibromide (Vol. I, p. 372) with sodium phenylhydrazine (*Michaelis*, *Lampe*, Ann. **274**, 316). In the air it oxidizes to phenylpyrazoline; with methyl iodide and alkali it forms **1-phenyl-2-methylpyrazolidine**, b.p. 175–180° (90 mm.). By reduction of the corresponding pyrazolidone **1-phenyl-3-methylpyrazolidine** is obtained (*Knorr*, *Duden*, Ber. **26**, 107). **1,3,5-Triphenyl-2-methylpyrazolidine**, m.p. 110°, is prepared by reduction of the methyl iodide addition product of triphenylpyrazole with sodium and alcohol.

3,5-Dimethylpyrazolidine, $(CH_3)_2C_3H_4{:}N_2H_2$, b.p. 141–143°, is formed together with 1,3-diaminopentane by electrolytic reduction of acetylacetone dioxime, $CH_3C(NOH)CH_2C(NOH)CH_3$ (*Tafel, Pfeffermann*, Ber. **36**, 219). This reaction corresponds to the formation of pinacols by reduction of ketones.

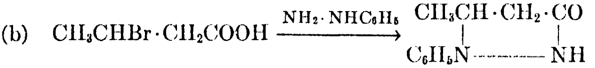
PYRAZOLIDINECARBOXYLIC ACIDS are obtained by reduction of pyrazolinecarboxylic acids (*Buchner*, Ann. **273**, 214), and are more stable than the latter. **4-Phenylpyrazolidine-3,5-dicarboxylic acid**, m.p. 220° (*Buchner, Perkel*, Ber. **36**, 3779).

OXO DERIVATIVES OF PYRAZOLIDINE. *1.* **Pyrazolidones** are prepared from β-halogenated fatty acids or α,β-olefincarboxylic acids with hydrazines. When phenylhydrazine is used, two reactions are possible, depending upon which amine group of the hydrazine reacts with the carboxyl group of the acid:



$$\text{(a)}\quad CH_3CH{:}CHCOOH \xrightarrow{NH_2\cdot NHC_6H_5} \begin{array}{l} CH_3CH\cdot CH_2\cdot CO \\ \quad|\qquad\qquad\quad| \\ NH\text{———}NC_6H_5 \end{array}$$

1-Phenyl-3-methyl-5-pyrazolidone



$$\text{(b)}\quad CH_3CHBr\cdot CH_2COOH \xrightarrow{NH_2\cdot NHC_6H_5} \begin{array}{l} CH_3CH\cdot CH_2\cdot CO \\ \quad|\qquad\qquad\quad| \\ C_6H_5N\text{———}NH \end{array}$$

1-Phenyl-5-methyl-3-pyrazolidone

The resulting isomers differ in that the 5-pyrazolidone derivative is completely basic, while the 3-pyrazolidone derivative shows acid characteristics also. Pyrazolidones are readily oxidized to pyrazolones; on reduction with sodium and alcohol they are partially converted to pyrazolidines (see above).

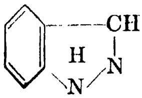
Pyrazolidone, $\overline{CO\cdot CH_2\cdot CH_2\cdot NH\cdot NH}$, m.p. 133–135°, from acrylic acid and hydrazine, is solely a base; it oxidizes readily to pyrazolone (*Rothenburg*, J.pr. **51**, 73). **1-Phenyl-5-pyrazolidone**, m.p. 78°, from β-halogenopropionic acid with sodium formylphenylhydrazine, or from acrylic acid with phenylhydrazine in toluene solution (*Stolz*, Ber. **28**, 626), has only basic properties and oxidizes to 1-phenyl-5-pyrazolone, m.p. 118° (p. 104). The isomeric **1-phenyl-3-pyrazolidone**, $\overline{CH_2\cdot CH_2\cdot CO\cdot NH\cdot NC_6H_5}$, m.p. 119–121°, from β-halogenopropionic acid with phenylhydrazine or from *as*-β-phenylhydrazinopropionic acid ester (G. P. 53834, 1889), has acid properties as well as basic; it oxidizes to 1-phenyl-3-pyrazolone (*Harries, Loth*, Ber. **29**, 517). **1-Phenyl-3-methyl-5-pyrazolidone**, m.p. 84°, b.p. 321°, from crotonic acid and phenylhydrazine, or from *s*-β-phenylhydrazinobutyric acid (Ger. Pat. 74858, 1893), is a base and oxidizes readily to 1-phenyl-3-methyl-5-pyrazolone; methylation converts it to **1-phenyl-2,3-dimethylpyrazolidone**, *hydroantipyrine*, m.p. 146°, which cannot be oxidized to antipyrine (*Knorr, Duden*, Ber. **26**, 103). **1-Phenyl-5-methyl-3-pyrazolidone**, m.p. 128°, from *as*-β-phenylhydrazinobutyric acid, has both acidic and basic properties; it oxidizes to 1-phenyl-5-methyl-3-pyrazolone (p. 108). **1-Phenyl-5,5-dimethyl-3-pyrazolidone**, m.p. 110°, from chloroisovaleric acid, and **1-phenyl-3,3-dimethyl-5-pyrazolidone**, m.p. 75°, from dimethylacrylic acid and phenylhydrazine; the 1,5,5,3-acid is split by boiling barium hydroxide solution to benzeneazoisovaleric acid, $C_6H_5N{:}N\cdot C(CH_3)_2CH_2COOH$ (*Montemartini*, Gazz. **27**, II, 368; *Prentice*, Ann. **292**, 284). **1,5-Diphenyl-4-hydroxy-3-pyrazolidone**, $\overline{C_6H_5N\cdot NH\cdot CO\cdot CH(OH)\cdot CHC_6H_5}$, m.p. 173°, is prepared by heating sodium phenylglycidate with phenylhydrazine. When heated alone or with $ZnCl_2$ it forms 1,5-diphenyl-3-pyrazolone (p. 108), water being eliminated (*Japp, Maitland*, J. **85**, 1490).

2. **Pyrazolidinediones** are cyclic hydrazides of malonic acids: **3,5-Pyrazolidinedione**, *malonohydrazide*, $\overline{CO\cdot CH_2\cdot CO\cdot NH\cdot NH}$, oil, from malonic ester and hydrazine (*Rothenburg*, J.pr. **51**, 43). **1-Phenyl-3,5-pyrazolidinedione**, *phenylmalonohydrazide*, m.p. 192°, from the ethyl ester of malonic acid monophenylhydrazide (*Michaelis, Burmeister*, Ber.**25**, 1506), from malonic acid ester, phenylhydrazine and sodium ethylate (*Conrad, Zart*, Ber. **39**, 2282) and from a mixture of malonic acid and acetylphenylhydrazine with PCl_3 (*Michaelis, Schenk*, Ber. **40**, 3568), is apparently a phenylhydroxypyrazolone; with $POCl_3$ it gives 1-*phenyl*-3-*chloro*-5-*pyrazolone*, m.p. 144°, and phenyldichloropyrazole (p. 96; *Michaelis, Röhmer*, Ber. **31**, 3003). **1-Phenyl-4,4-dimethyl-3,5-pyrazolidinedione**, m.p. 176°, from dimethylmalonic acid, acetylphenylhydrazine, and PCl_3 (*Michaelis, Schenk*, Ber. **40**, 3569; **41**, 3865).

2. INDAZOLES

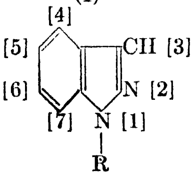
As the indoles are benzo derivatives of the pyrroles, so the indazoles are benzo derivatives of the pyrazoles.

The question of the constitution of unsubstituted indazole must be left open, since the imine hydrogen, as in monocyclic pyrazoles, seems to oscillate between the two nitrogen atoms. The following structural formula for indazole indicates this:



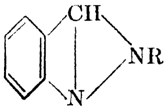
Two series of N-*alkylindazoles* are known; their structure is determined unequivocally by their manner of preparation. The 1-*alkyl*- or *arylindazoles* (preparation, pages 114 *ff.*) correspond to formula I, while for the isomeric 2-*alkyl*- or *arylindazoles* (preparation, p. 114) formula IIa or formula IIb is possible. Several derivatives of indazole, such as indiazone oximes (p. 116) and diazoindazoles (p. 116), are derived from the indiazene form (formula III), corresponding to the indolenine form of indole:

(I)

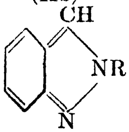


1-Alkylindazoles (formerly called isoindazoles)

(IIa)

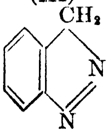


(IIb)



2-Alkylindazoles

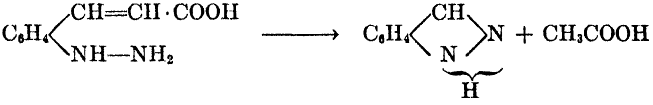
(III)



Indiazene

While the constitution of 1-alkylindazoles is certain, it is difficult to choose between IIa and IIb for 2-alkylindazoles. Spectroscopic data point to formula IIb (*v. Auwers*, Ann. **437,** 70). With formula IIb the 2-alkylindazoles are analogous to naphthalenes (*v. Auwers, Frühling*, Ann. **422,** 192, 206; *v. Auwers, Krollpfeiffer*, Ann. **430,** 230). In view of the several remarkable methods for synthesizing this ring, the indazole ring system is one of the most interesting of the heterocyclic series.

Indazoles are prepared: (*1*) From the *o*-hydrazinocinnamic acids by heating (*E. Fischer, Tafel*, Ann. **227,** 303):

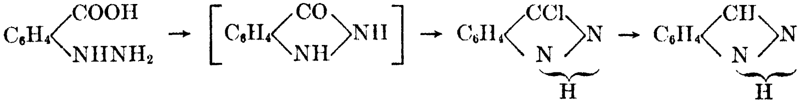


$$C_6H_4\begin{cases}CH{=}CH\cdot COOH\\ NH{-}NH_2\end{cases} \longrightarrow C_6H_4\begin{cases}CH\\ \underbrace{N}_{H}\end{cases}\!\!>N + CH_3COOH$$

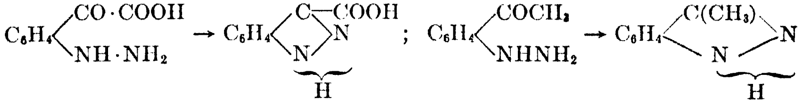
o-Hydrazinocinnamic acid Indazole

It is noteworthy that a lactam-like anhydride of hydrazinocinnamic acid is not formed in this reaction; such a compound would contain a seven-membered ring. Gentle oxidation of *o*-hydrazinocinnamic acid gives 3-indazoleacetic acid (see p. 117).

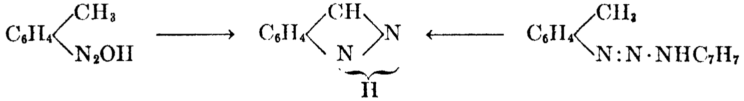
(*2*) *o*-Hydrazinobenzoic acid is converted when heated with $POCl_3$ under pressure to 3-chloroindazole, which is reduced to indazole by zinc and hydrochloric acid (*Fischer, Seuffert,* Ber. **34,** 796):



(*3*) Indazoles are obtained by splitting off water from *o*-hydrazinoacetophenones or *o*-hydrazinophenylglyoxylic acids:

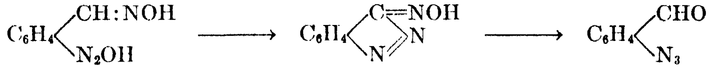


(*4*) Indazoles are also formed from *o*-methyldiazobenzenes (*Michel, Grandmougin,* Ber. **26,** 2349; *Bamberger,* Ann. **305,** 289):



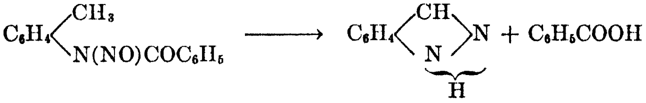
o-Toluenediazo-hydroxide Indazole *o*-Toluene-diazotoluide

A large number of indazoles substituted in the benzene nucleus have been obtained by this method. The diazohydroxide from *o*-toluidine when boiled in acid solution gives only *o*-cresol, but in neutral solution it forms 3-tolueneazoindazole and a little indazole; substituted benzeneazoindazoles are usually obtained in the decomposition of *o*-methylated diazobenzenes in strongly alkaline solution, in which the indazole produced couples with the diazo compound which has not yet decomposed. Only the diazo compounds from nitrated *o*-methylanilines react immediately to give indazoles, which are obtained in good yield by boiling these compounds with mineral acids or by treating them with glacial acetic acid (*Noelting,* Ber. **37,** 2556). If *o*-aminobenzaldoximes are diazotized, indiazone oximes are formed; these are readily isomerized by water or alkali to *o*-triazobenzaldehydes (*Bamberger, Demuth,* Ber. **34,** 1309):



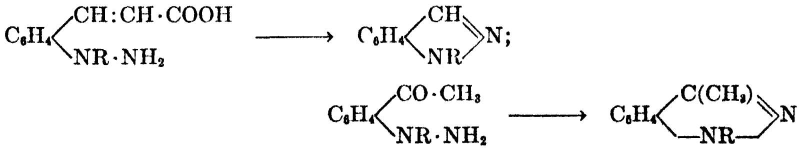
o-Diazobenzaldoxime Indiazone oxime, m.p. 160° *o*-Triazobenzaldehyde

(*5*) Indazoles are produced smoothly from the nitroso derivatives of acylated *o*-methylanilines by warming in benzene solution (*Jacobson, Huber,* Ber. **41,** 660):

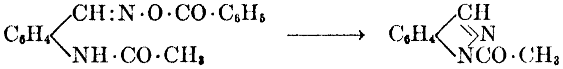


The following syntheses give 1-**alkyl**-, 1-**aryl**- or 1-**acylindazoles**:

(*1*) From *o*-*as*-alkylhydrazinocinnamic acids or *o*-*as*-alkylhydrazinacetophenones:

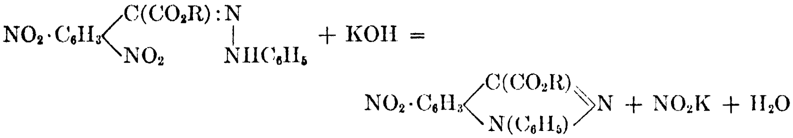


(*2*) 1-Acylindazoles can be obtained from certain acylated *o*-aminobenzaldoximes or ketoximes with alkali carbonate (*v. Auwers*, Ber. **58**, 2081; *v. Auwers*, *Frese*, Ann. **450**, 273):



$$C_6H_4\left<\begin{matrix}CH{:}N\cdot O\cdot CO\cdot C_6H_5\\ NH\cdot CO\cdot CH_3\end{matrix}\right. \longrightarrow C_6H_4\left<\begin{matrix}CH\\ NCO\cdot CH_3\end{matrix}\right>N$$

(*3a*) From the phenylhydrazones of aromatic carboxyl compounds which contain several nitro groups, such as the phenylhydrazone of *o,p*-dinitrophenylglyoxylic acid ester, which gives 1-phenylnitroindazole-3-carboxylic acid ester (*Meyer*, Ber. **22**, 319):



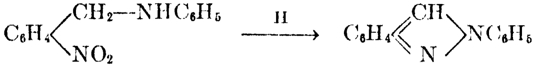
$$NO_2\cdot C_6H_3\left<\begin{matrix}C(CO_2R){:}N\\ \qquad\qquad |\\ NO_2\qquad NHC_6H_5\end{matrix}\right. + KOH =$$

$$NO_2\cdot C_6H_3\left<\begin{matrix}C(CO_2R)\\ N(C_6H_5)\end{matrix}\right>N + NO_2K + H_2O$$

(*3b*) By a similar conversion 1-*benzoyl-5-nitroindazole* is formed from the benzoylhydrazone of 2-chloro-5-nitrobenzaldehyde, HCl being eliminated (*Meisenheimer*, *Senn*, Ber. **59**, 199).

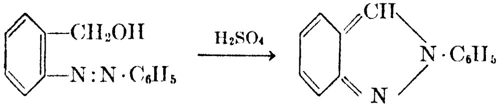
Indazoles having an alkyl, aryl or acyl group in the 2-position are prepared by the following methods:

(*a*) By reduction of *o*-nitrobenzylanilines (Vol. III, p. 262) 2-phenylindazoles are formed (*Paal*, Ber. **24**, 961; *Busch*, Ber. **27**, 2899):



$$C_6H_4\left<\begin{matrix}CH_2\text{—}NHC_6H_5\\ NO_2\end{matrix}\right. \xrightarrow{H} C_6H_4\left<\begin{matrix}CH\\ N\end{matrix}\right>NC_6H_5$$

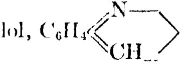
(*b*) 2-Phenylindazole is also obtained from *o*-benzeneazobenzyl alcohol by treatment with 50% sulfuric acid (literature: *Bamberger*, Ber. **44**, 1967):



(*c*) By an unusual reaction *Bz*-chlorinated 2-phenylindazole is produced by the action of PCl_5 on *o*-benzeneazobenzoic acid instead of the expected acid chloride (literature: *Bamberger*, Ber. **44**, 1967).

Properties.—The indazoles are usually crystalline, slightly basic compounds, but they also form salts with metals: Ag, Na (*v. Auwers*, *Schaich*, Ber. **54**, 1750). They are quite resistant to oxidation; chromic acid splits 2-phenylindazole to azobenzenecarboxylic acid. Hydroindazoles are formed with difficulty. The free imine group is readily alkylated and acylated. Alkylating agents convert indazole to N-alkylindazoles and, with an excess of alkyl halide, to indazolium compounds. The type of N-alkyl derivative formed (whether 1-alkyl or 2-alkylindazole) depends: (*1*) on the method of alkylation, (*2*) on the nature of the alkyl halide, and (*3*) on the temperature (*v. Auwers*, *Schaich*, Ber. **54**, 1738). When indazole is heated directly with alkyl halides 2-alkyl derivatives are formed preferentially. Pure 1-alkylindazoles are obtained also by ring-synthesis (p. 113). For acylindazoles, see below. Indazole and the *Bz*-substituted indazoles couple with diazobenzenes to give benzeneazoindazoles, and with benzaldehyde to give benzylidene-*bis*-indazole, $C_6H_5CH(C_7H_5N_2)_2$.

Indazole is nitrated by concentrated HNO_3 to 5-nitroindazole (see below); it is sulfonated by fuming sulfuric acid (*v. Auwers*, *Kleiner*, J.pr. **118**, 67). With $NaNO_2$ indazole gives nitrosoindazole, m.p. 74°. For the action of halogens on indazoles, see halogen derivatives of indazole.

INDAZOLE, m.p. 146°, b.p. 270°, is prepared from its carboxylic acid (p. 117), from *o*-hydrazinocinnamic acid, from chloroindazole, from benzoyl-*o*-tolylnitrosamine, from *o*-toluenediazonium chloride with aqueous sodium hydroxide (p. 113), and from *o*-aminobenzaldehyde by diazotization (*Eliasberg, Friedländer*, Ber. **25**, 1754). 2-Indazolol,  $C_6H_4\left<\begin{matrix}N—\\CH\end{matrix}\right>NOH$, m.p. 139°, strongly acid, from *o*-azidobenzaldoxime (Vol. III, p. 331) by boiling with aqueous sodium hydroxide, is reduced to indazole with zinc and hydrochloric acid (*Bamberger, Demuth*, Ber. **35**, 1891).

N-ALKYLINDAZOLES. 2-Alkylindazoles are stronger bases and boil at a higher temperature than 1-alkylindazoles (*v. Auwers, Düesberg*, Ber. **53**, 1179; *v. Auwers, Pfuhl*, Ber. **58**, 1363). The picrates of the 2-alkylindazoles melt higher than those of the isomeric 1-alkylindazoles.

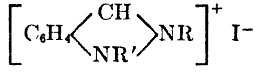
1-Methylindazole, m.p. 60°, b.p. 231°, from indazole and methyl iodide in the presence of sodium methylate (*v. Auwers, Düesberg*, Ber. **53**, 1196). **2-Methylindazole**, m.p. 56°, b.p. 261°, from indazole and methyl iodide or by decarboxylation of 2-methylindazole-3-carboxylic acid (*v. Auwers, Düesberg*, Ber. **53**, 1196). **1-Ethylindazole**, b.p. 127° (21 mm.). **2-Ethylindazole**, m.p. 30°, b.p. 268°. **2-Propylindazole**, m.p. 29°, b.p. 144° (14 mm.) (*v. Auwers, Pfuhl*, Ber. **58**, 1360). **1-Benzylindazole**, m.p. 64.5°, b.p. 193° (15 mm.). **2-Benzylindazole**, m.p., 71°, b.p. 219° (15 mm.) (*Fischer, Blochmann*, Ber. **35**, 2318).

OTHER ALKYLINDAZOLES. 7-Methyl-, 5-methyl- and 5,7-**dimethylindazole** (for the numbering, see p. 112), m.p. 138°, 115° and 134°, are obtained from the xylidines and from mesidine by method *4* or *5* (*Bamberger*, Ann. **305**, 308, 363; *Jacobson, Huber*, Ber. **41**, 666). 3-**Methylindazole**, m.p. 113°, b.p. 281°, from *o*-hydrazinoacetophenone, reacts with acetyl chloride to give 2-acetyl-3-methylindazole, m.p. 72° (*v. Auwers, v. Mayenburg*, Ber. **24**, 2380), and with methyl iodide to give 2,3-**dimethylindazole**, m.p. 80°. 1,3-**Dimethylindazole**, m.p. 36° (*v. Auwers, Düesberg*, Ber. **53**, 1202). 2-**Phenylindazole**, m.p. 84°, b.p. 345°, is formed from *o*-nitrobenzylaniline by reduction (see above) (*v. Auwers, Strödter*, Ber. **59**, 535), and from *o*-benzeneazobenzyl alcohol by heating with H_2SO_4 (see above). 2-Phenylindazole is oxidized by CrO_3 to azobenzenecarboxylic acid; it forms a methyl iodide addition product, m.p. 188° (*Paal*, Ber. **24**, 3058; *Paal, Lücker*, Ber. **27**, 48). 3-**Phenylindazole**, m.p. 108° (116°), is obtained by reduction of *o*-diazobenzophenone (*v. Auwers*, Ber. **29**, 1265; *v. Auwers, Hüttenes*, Ber. **55**, 1113; *v. Auwers, Schaum*, Ber. **62**, 1671).

N-ACYLINDAZOLES. Direct acylation of indazole usually produces both 1- and 2-acylindazoles (*v. Auwers*, Ber. **52**, 1331; Ann. **450**, 273; *Meisenheimer, Diedrich*, Ber. **57**, 1715). Pure 1-acylindazoles are obtained by ring-synthesis according to equations *2* and *3b* on p. 114. 2-Acylindazoles are best prepared by acylation of indazoles at moderate temperatures or by acylation of their silver salts (*v. Auwers*, Ber. **58**, 2081). The labile 2-acyl derivatives rearrange readily to 1-acyl derivatives (*v. Auwers, Demuth*, Ann. **451**, 282); the principal cause of this wandering of the acyl group is the tendency of the *o*-quinoid system (formula IIb, p. 112) to pass into the benzenoid system (formula I, p. 112).

1-**Acetylindazole**, m.p. 42° (*v. Auwers, Frese*, Ann. **450**, 289). 2-**Acetylindazole**, m.p. 106°. 1-**Benzoylindazole**, m.p. 93°, according to equation *2* (p. 114). 1-**Acetyl**-5,7-**dimethylindazole**, m.p. 72°, by isomerization of the 2-acetyl derivative, m.p. 117° (*v. Auwers, Ernecke, Wolter*, Ann. **478**, 156). 4-, 5-, 6-, 7-**Nitroindazole**, m.p. 203°, 208°, 181°, 187°, from the diazo derivatives of the nitro-*o*-toluidines (see above). 1,3-**Diphenyl**-5-**nitroindazole**, m.p. 181°, from the phenylhydrazone of 2-chlorobenzophenone (*Anschütz*, Ann. **454**, 112).

INDAZOLIUM COMPOUNDS. These quaternary ammonium compounds are formed by heating N-alkylindazoles with alkyl halides at 100° (bomb). Their behavior indicates that they have the formula:



$$\left[C_6H_4\left<\begin{matrix}CH\\NR'\end{matrix}\right>NR\right]^+ I^-$$

Thus 1-methyl- and 2-methylindazole give the same dimethylindazolium iodide with methyl iodide, and two isomeric indazolium compounds with other alkyl halides.

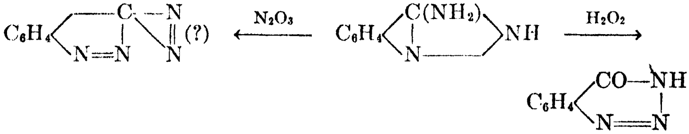
When heated over the melting point the indazolium compounds decompose to alkyl halides and N-alkylindazoles. Generally 1-alkylindazoles result, unless the alkyl group in the 2-position is attached much more firmly. (Tables of the decomposition products: *v. Auwers, Pfuhl*, Ber. **58**, 1362; *v. Auwers, Düsterdick, Kleiner*, Ber. **61**, 101.)

1,2-**Dimethylindazolium chloride**, m.p. 137°; **bromide**, m.p. 113°; **iodide**, m.p. 187°. 1-**Methyl-2-ethylindazolium chloride**, m.p. 186°; **bromide**, m.p. 197°; **iodide**, m.p. 173°. (Other indazolium compounds: *v. Auwers, Pfuhl*, Ber. 58, 1367.)

3-**AZO, AMINO**- and **DIAZOINDAZOLES**. 3-Azo derivatives of the indazoles are prepared by the action of alkaline diazo solutions on the indazoles; they are also formed together with indazoles by the reaction of *o*-methylated diazonium salts with alkali (see p. 113, method *4*). 3-**Benzeneazoindazole**, $C_7H_5N_2$-(N:NC_6H_5), orange-yellow needles, m.p. 191°. 3-**Tolueneazoindazole**, m.p. 211°, from *o*-diazotoluene. 3-**Mesityleneazodimethylindazole**, m.p. 258°, from diazomesidine. 3-(**Nitromethylbenzeneazo**)-**nitroindazole**, see *Noelting*, Ber. **37**, 2579.

On reduction these azo compounds are split to primary aromatic amines and 3-aminoindazoles. 3-**Aminoindazole**, $C_7H_5N_2(NH_2)$, m.p. 154°, is also obtained from *o*-aminobenzonitrile by diazotization and subsequent reduction, by rearrangement of the *o*-cyanophenylhydrazine first formed (*Reissert, Grube*, Ber. **42**, 3716). 5-**Methyl**- and 5,7-**dimethyl**-3-**aminoindazole**, m.p. 191° and 151°. With nitrous acid the aminoindazoles form relatively stable diazonium hydroxides: $C_7H_5N_2(N_2OH)$, *etc.*, which are converted by elimination of water to more stable inner anhydrides, the indazoletriazolenes (I). **Indazoletriazolene**, 3-*diazoindazole*, yellow needles, m.p. 106°; the latter couple readily with phenols and naphthols to give hydroxyazo dyes; with the hydrogen halides they give 3-halogenoindazoles. 5-**Aminoindazole**, m.p. 181° (*Fries*, Ann. **454, 306**, 310); 1,3-**diphenyl**-5-**aminoindazole**, *hydrochloride* m.p. 312°, both from the corresponding nitro compounds. When the aminoindazoles are oxidized with hydrogen peroxide, bichromate or the like in acid solution, 4-oxo-3,4-dihydro-1,2,3-benzotriazines, benzazimides (II), are formed (*Bamberger*, Ann. **305**, 289; Ber. **32**, 1773, 1797; *Hantzsch*, Ber. **35**, 892):

(I)

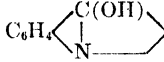
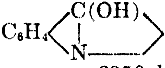


(II)

In alkaline solution the aminoindazoles are oxidized even by the oxygen of the air to azoindazoles: **Azoindazole**, $(C_7H_5N_2)N{:}N(C_7H_5N_2)$, dark red needles, m.p. 229° (*Bamberger, Wildi*, Ber. **39**, 4276).

HALOGEN DERIVATIVES OF INDAZOLES. Indazole is readily substituted by chlorine and bromine. The principal products are 3,5-dihalogenoindazoles; when the silver salt of indazole is used, 3-monohalogenated derivatives are obtained. 5-Monohalogen derivatives result from the action of chlorine and bromine on acetylindazole (*v. Auwers, Lange*, Ber. **55**, 1148).

3-**Chloroindazole**, m.p. 148°, from diazoindazole (see above) with hydrochloric acid, from *o*-hydrazinobenzoic acid by heating with $POCl_3$ under pressure or from the **Ag** salt of indazole by chlorination (*v. Auwers, Lange*, Ber. **55**, 1158); the chlorine atom is very firmly attached. 3-**Bromoindazole**, m.p. 142° (*ibid.*, p. 1165); 3-**iodoindazole**, m.p. 142°. 5-**Chloroindazole** exists in two forms, m. p. 120° and 144°. 5-**Bromoindazole,** m.p. 125° and 133°. For other mono- and dihalogenoindazoles, see *v. Auwers, Lange*, Ber. **55**, 1157 *ff*.

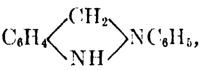
2-Phenyl-3-**indazolol**,  $C_6H_4\langle C(OH)\rangle NC_6H_5$, m.p. 218°, is prepared from *o*-benzeneazobenzaldehyde acetal, $C_6H_5N{:}NC_6H_4CH(OCH_3)_2$, by saponification with dilute sulfuric acid (*Freundler, de Laborderie*, Bull. [IV], **1**, 234). 2-*o*-**Carboxyphenyl**-3-**indazolol**,  $C_6H_4\langle C(OH)\rangle NC_6H_4[2]COOH$, m.p. 228°, is obtained in the form of its lactone, m.p. 295°, by the action of $POCl_3$ on *o*-hydrazobenzoic acid (*Carré*, C.r. **143**, 54), or from 2,2′-azoxybenzaldehyde by boiling with glacial acetic acid (*Bamberger, Lublin*, Ber. **42**, 1706). **6-Indazolol, m.p.** 215-216°, from the corresponding nitroindazole (*Witt, Noelting, Grandmougin*, Ber. **25**, 3152).

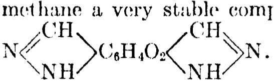
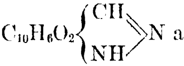
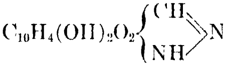
INDAZOLE KETONES. **3-Benzoylindazole**, m.p. 189°, from 3-cyanoindazole and C_6H_5MgBr (*Meisenheimer, Diedrich*, Ber. **57**, 1719); also, **3-acetylindazole**, m.p. 182°.

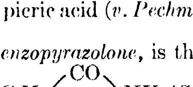
INDAZOLECARBOXYLIC ACIDS. 1-Indazolecarboxylic acid ethyl ester, b.p. 156° (10 mm.), from indazole and chloroformic ester (*v. Auwers, Frese*, Ann. **450**, 273). **3-Indazolecarboxylic acid,** m.p. 295° (dec.), is prepared from *o*-hydrazinophenylglyoxylic acid, which is obtained from isatinic acid, thus constituting a transition from the indole to the indazole series (*Schad*, Ber. **26**, 217); its *nitrile*, m.p. 140°, is produced by the action of nitrous acid on *o*-amino-α-tolunitrile (*Pschorr, Hoppe*, Ber. **43**, 2544). The indazolecarboxylic acid decomposes on heating into indazole and CO_2. N-Alkyl derivatives of 3-indazolecarboxylic acid: *v. Auwers, Dereser*, Ber. **52**, 1340.

3-Indazoleacetic acid, m.p. 169° (dec.), is prepared by mild oxidation of *o*-hydrazinocinnamic acid; when heated it yields 3-methylindazole and CO_2.

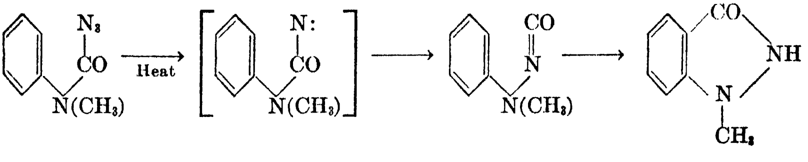
1,3-Indazoledicarboxylic acid dimethyl ester, m.p. 175° (*v. Auwers, Strödter*, Ber. **59**, 537), from 3-indazolecarboxylic acid methyl ester and chloroformic acid methyl ester.

INDAZOLINES. 2-Phenylindazoline,  $C_6H_4{<}\begin{matrix}CH_2\\NH\end{matrix}{>}NC_6H_5$, m.p. 138°, is formed by reduction of phenylindazole with Na and alcohol, and is reconverted to the indazole by mild oxidation ($FeCl_3$); *Bz*-**nitro-1-phenylindazoline-3-carboxylic acid,** m.p. 235°, by similar reduction of phenylnitroindazolecarboxylic acid (*Schulhöfer*, Ann. **264**, 149).

Products which appear to be benzo- and naphthodihydropyrazoles are obtained by the reaction of quinones with diazomethane. From benzoquinone and diazomethane a very stable compound is formed which seems to have the formula:  $N{\lessdot}\begin{matrix}CH\\NH\end{matrix}{>}C_6H_4O_2{<}\begin{matrix}CH\\NH\end{matrix}{\gtrdot}N$. 1,4-Naphthoquinone and naphthazarin give these naphthopyrazoles:  $C_{10}H_6O_2\left\{\begin{matrix}CH\\NH\end{matrix}\right.{\gtrdot}N$ and  $C_{10}H_4(OH)_2O_2\left\{\begin{matrix}CH\\NH\end{matrix}\right.{\gtrdot}N$. The tri-acetyl derivative of the latter compound is oxidized by nitric acid to 4,5-*pyrazoledicarboxylic acid* (p. 100). Similar products are obtained from diazomethane and trinitrobenzene or picric acid (*v. Pechmann, Seel*, Ber. **32**, 2292; *v. Pechmann*, Ber. **33**, 627).

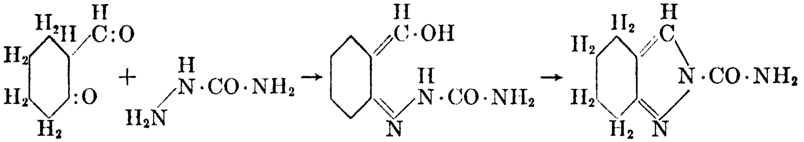
3-Indazolone, *benzopyrazolone*, is the inner anhydride or lactazam of *o*-hydrazinobenzoic acid,  $C_6H_4{<}\begin{matrix}CO\\NH\end{matrix}{>}NH$ (*Spring*, Ann. **213**, 333; *cf. Thode*, J.pr. **69**, 94). **1-Phenylindazolone,** $C_7H_5ON_2(C_6H_5)$, m.p. 209°, from *o*-aminobenzoylphenylhydrazine with N_2O_3 (*König, Reissert*, Ber. **32**, 782). **7-Nitro-2-phenyl-3-indazolone,** from 3-nitro-2-phenylhydrazinobenzoic acid ester (*Rupe*, Ber. **30**, 1100).

A general method for the preparation of **1-alkyl-** or **1-aryl-3-indazolones** has been devised by *Stollé* (J.pr. **116**, 192). It consists in the rearrangement of N,N-arylalkylcarbamic acid azides RR′N·CON_3 into 1-alkyl-3-indazolones by elimination of nitrogen under the influence of heat:



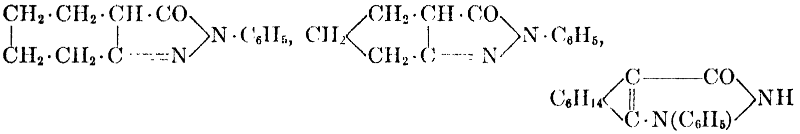
1-Methyl-3-indazolone, m.p. 154°; **1-ethylindazolone,** m.p. 134°. (Others: *Stollé*, J.pr. **117**, 185).

4,5,6,7-TETRAHYDROINDAZOLES have been obtained by *Wallach* (Ann. **329**, 109) by the action of hydrazine or semicarbazide on the hydroxymethylene derivatives of hydroaromatic ketones (*cf. v. Auwers, Buschmann, Heidenreich*, Ann. **435**, 277):

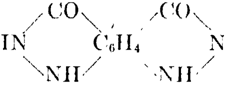


4,5,6,7-Tetrahydroindazole, m.p. 84°, b.p. 151° (14 mm.) (*v. Auwers, Buschmann, Heidenreich*, Ann. **435**, 303); picrate, m.p. 156° (*ibid.*, p. 277); for other derivatives, see *v. Auwers, v. Sass, Willekindt*, Ann. **444**, 209; *v. Auwers, Conrad, Ernecke, Ottens*, Ann. **469**, 57.

This class of compounds also includes the dicyclic pyrazolone derivatives obtained from cycloketone-β-carboxylic acid esters, such as oxocyclopentane- and oxocyclohexane-2-carboxylic acid esters, and camphocarboxylic acids esters (Vol. II, p. 294), with phenylhydrazine:

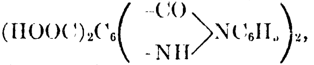


Camphoroxalic acid ester and phenylhydrazine give phenylcamphopyrazolecarboxylic acid ester (*cf. Wahl*, Ber. **32**, 1987; *Dieckmann*, Ann. **317**, 27).



$$HN\left\langle\begin{matrix}CO\\NH\end{matrix}\right\rangle C_6H_4\left\langle\begin{matrix}CO\\NH\end{matrix}\right\rangle NH$$

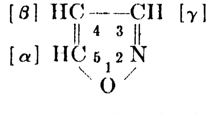
Dihydrobenzodipyrazolone, m.p. 257°, is prepared from succinylsuccinic acid ester and hydrazine (*v. Rothenburg*, Ber. **27**, 472).



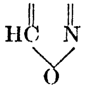
$$(HOOC)_2C_6\left(\left\langle\begin{matrix}CO\\NH\end{matrix}\right\rangle NC_6H_5\right)_2$$

N,N′ - Diphenyldicarboxybenzodipyrazolone, from hydroquinonetetracarboxylic acid ester and phenylhydrazine [*Nef*, Am. Chem.J. **12** (1890), 379].

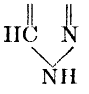
3. ISOXAZOLES



The isoxazole ring is a furan ring in which one of the methine groups adjacent to the O is replaced by N. It resembles the pyrazole ring more closely, as may be seen by a comparison of the two structural formulas:

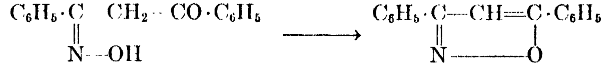


Isoxazole



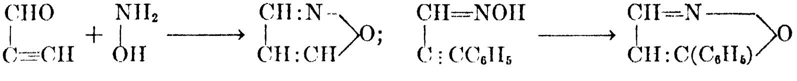
Pyrazole

This similarity is also apparent in their synthesis. (*1*) As the pyrazoles are obtained from the hydrazones of β-dioxo compounds, so the isoxazoles are prepared from the monoximes of β-diketones and β-oxoaldehydes or hydroxymethylene ketones by elimination of water (*Claisen*, Ber. **24**, 3906):



Benzoylacetophenone monoxime 3,5-Diphenylisoxazole

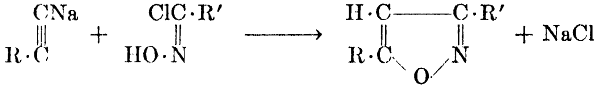
(*2*) Isoxazoles are formed from propiolaldehydes and hydroxylamine (*Claisen*, Ber. **36**, 3665; **44**, 1161; *Moureu*, *Delange*, C.r. **138**, 1339):



Similarly acylacetylenes and phenylhydrazine give 3,5-disubstituted isoxazoles (*Moureu*, *Brachin*, C.r. **137**, 795; **139**, 294).

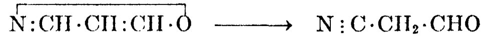
With unsymmetric dicarbonyl compounds, two isomeric isoxazoles are usually produced. To obtain isoxazoles of certain constitution the synthesis from unsymmetric 1,3-diketones or acylacetylenes and phenylhydrazine must be used with caution, since it is not known which of the two oxo groups will react first, or, when acylacetylenes are used, whether the conversion of the oxo group to an oxime or the addition of hydroxylamine to the acetylene bond takes place more rapidly.

(*3*) A completely unequivocal synthesis of isoxazoles consists in the reaction of *hydroxamic acid chlorides* with *sodium derivatives* of *acetylenes* (*Weygand*, *Bauer*, Ann. **459**, 123):

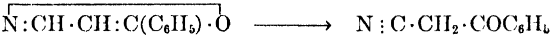


For the formation of isoxazoles from nitroparaffins by treatment with alkali, see *Dunstan*, *Dymond*, J. **1891**, 410. This method is especially useful for the preparation of triarylisoxazoles (*Heim*, Ber. **44**, 2020; *Meisenheimer*, *Weibezahn*, Ber. **54**, 3195).

Properties.—The isoxazoles, like the pyrazoles, are weak bases. While the 3,5-disubstituted isoxazoles are very resistant to alkali, the isoxazoles with a free 3-position rearrange to β-oxo nitriles in alcoholic alkali, even in the cold:

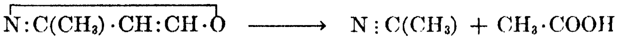


Isoxazole Malonaldehydic acid nitrile



5-Phenylisoxazole Benzoylacetonitrile

Isoxazoles with substituted 3-position but free 5-position are decomposed when warmed with alcoholic potassium hydroxide into carboxylic acids and nitriles (*Claisen*, Ber. **36**, 3672):



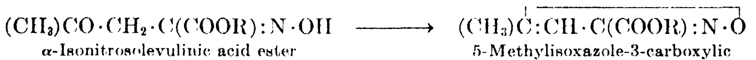
For ring-fission by reduction, see *Claisen*, Ber. **24**, 3912.

ISOXAZOLE, b.p. 95°, d^{14} 1.078 (*v. Auwers*, Ber. **57**, 463), very fluid liquid with an odor like pyridine, forms crystalline compounds with $PtCl_4$ and with $CdCl_2$ (*Claisen*, Ber. **36**, 3665). **5-Methylisoxazole**, b.p. 122°, and **3-methylisoxazole**, b.p. 118°, are prepared together from hydroxymethyleneacetone and NH_2OH; the 5-methyl derivative is also obtained from tetrolaldehyde or its acetal with hydroxylamine (*Claisen*, Ber. **44**, 1161). **3,4,5-Trimethylisoxazole**, m.p. 3.5°, b.p. 248°, from the monoxime of methylacetylacetone and from nitroethane with alkali (*Dunstan*, *Dymond*, J. **1891**, 410). **5-Phenylisoxazole**, m.p. 23°, b.p. 247°, is formed from phenylpropiolaldoxime in cold aqueous sodium hydroxide solution and rearranges in sodium ethylate solution to phenacyl cyanide; it is also obtained together with the isomeric 3-**phenylisoxazole** from hydroxymethyleneacetophenone with NH_2OH (*Claisen*, Ber. **36**, 3673). 3-**Methyl-5-phenylisoxazole**, m.p. 68°, b.p. 125° (19 mm.), from benzoylacetone or phenylacetylacetylene (*Moureu*, *Brachin*, C.r. **137**, 795), is converted by heating with alcoholic ammonia into 3-methyl-5-phenylpyrazole (p. 94). 3,4,5-**Triphenylisoxazole**, m.p. 212°, from phenylnitromethane and benzaldehyde or from 7-nitrostilbene by treatment with warm aqueous sodium hydroxide solution (*Heim*, Ber. **44**, 2020; *Meisenheimer*, *Weibezahn*, Ber. **54**, 3195). For other triarylisoxazoles, see *Meisenheimer*, *Weibezahn*, Ber. **54**, 3200.

4-**Nitroisoxazole**, m.p. 46–47°, from nitromalondialdehyde (Vol. I, p. 591) with 1 mol hydroxylamine, is decomposed by water to nitromalonaldehydic acid nitrile [*Hill*, *Hale*, Am.Chem.J. 29 (1903), 253]. 3-**Phenyl-4-nitroisoxazole**, m.p. 116°, is formed from cinnamaldehyde with nitrous gases and is split by alcoholic potassium hydroxide to benzonitrile and nitroacetic ester; when reduced with Al-amalgam it gives 3-**phenyl-4-aminoisoxazole**, b.p. 179° (12 mm.), (*Wieland*, Ann. **328**, 245). 3-(4′-**Nitrophenyl**)-5-**phenyl-4-nitroisoxazole**, m.p. 199°, from benzalacetophenone with N_2O_3 (*Wieland*, Ann. **328**, 224).

For molar refraction and specific weight of a series of isoxazoles, see *v. Auwers*, Ber. **57**, 463.

ISOXAZOLECARBOXYLIC ACIDS. The esters are prepared from the oximes of α,γ-dioxo acid esters:



$$(CH_3)CO\cdot CH_2\cdot C(COOR){:}N\cdot OH \longrightarrow (CH_3)C{:}CH\cdot C(COOR){:}N\cdot O$$

α-Isonitrosolevulinic acid ester

5-Methylisoxazole-3-carboxylic acid ester

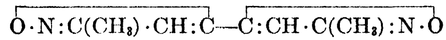
5-**Methylisoxazole-3-carboxylic acid**, m.p. 176°, and 3-**methylisoxazole-5-carboxylic acid**, m.p. 211°; their esters are obtained together from acetylpyruvic acid ester and NH_2OH. The free acids do not split into CO_2 and isoxazole when heated, but decompose completely (*Claisen*, Ber. **24**, 3908).

5-**Methylisoxazole-3,4-dicarboxylic acid**, m.p. 183° (dec.), is obtained in the form of its diethyl ester, m.p. 57°, by the action of fuming nitric acid on mono- or diacetylsuccinic acid ester (*Schmidt*, *Widmann*, Ber. **42**, 1869).

BIISOXAZOLES are formed from oxalyldiketones and hydroxylamine:

$$CH_3\cdot CO\cdot CH_2\cdot CO\cdot CO\cdot CH_2\cdot CO\cdot CH_3 \longrightarrow$$

2,4,5,7-Octanetetrone

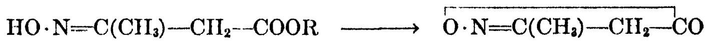


$$O\cdot N{:}C(CH_3)\cdot CH{:}C{-}C{:}CH\cdot C(CH_3){:}N\cdot O$$

3,3′-Dimethyl-5,5′-biisoxazole

The intermediate product in this reaction, 5-acetoacetyl-3-methylisoxazole, is also obtained by condensation of 3-methylisoxazole-5-carboxylic acid ester with acetone (*Claisen*, Ber. **24**, 3910).

ISOXAZOLONES, OXOISOXALINES. The isoxazolones are oxo derivatives of the hypothetical dihydroisoxazole or isoxazoline; they are analogous to the pyrazolones. The 5-isoxazolones are easily accessible, being obtained from the oximes of the β-oxo carboxylic acid esters by elimination of alcohol [*Claisen*, *Zedel*, Ber. **24**, 140; *Schiff*, *Viciani*, Ber. **30**, 1159; *Erlenbach*, Ann. **269**, 33; *Oliveri-Mandalá*, Atti accad.Lincei [5] **18** (1909), II, 141]:

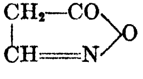


$$HO\cdot N{=}C(CH_3){-}CH_2{-}COOR \longrightarrow O\cdot N{=}C(CH_3){-}CH_2{-}CO$$

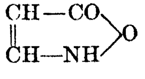
Oximes of isoxazolone derivatives are formed by the action of hydroxylamine hydrochloride on glyoxal, methylglyoxal, phenylglyoxal or the like (or their oximes) (*cf. Scholl*, Ber. **30**, 1287).

Like the pyrazolones (p. 103), the isoxazolones have several possible structures:

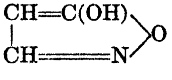
(I)



(II)



(III)



The isoxazolones have a decidedly acid character; they decompose alkaline earth carbonates in the cold, and form salts not only with metals, but also with ammonia and primary amines. The composition of these salts is variable (see below). The methylisoxazolones prepared from the silver salts with methyl iodide or from the isoxazolones themselves with diazomethane split methylamine when distilled with caustic alkali; the methyl group appears to be attached to the N, and the compounds are therefore derived from formula II above [*Uhlenhuth*, Ann. **296,** 37; *Oliveri-Mandalá*, *Coppola*, Atti accad. Lincei [5] **20** (1911), I, 244].

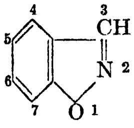
3-**Methyl-5-isoxazolone,** m.p. 170°, from acetoacetic ester oxime. Ba-salt, $(C_8H_7O_3N_2)_2Ba + 1^1/_2 H_2O$, ammonium salt, $(C_8H_7O_3N_2)NH_4$, both readily soluble in H_2O and alcohol; methyl derivative, $(C_8H_7O_3N_2)CH_3$, m.p. 75° (*Uhlenhuth*, Ann. **296,** 46). Condensation of acetoacetic ester oxime in the presence of benzenediazonium salts gives the phenylhydrazone of 3-methyl-4-oxo-5-isoxazolone, $(C_4H_3NO_2){:}NNHC_6H_5$, m.p. 192°. Acetoacetic ester oxime and ketones or aldehydes form compounds such as **isopropylidene-** and **benzylidenemethyl-5-isoxazolone,** $(C_4H_3NO_2){:}C(CH_3)_2$, m.p. 121°, and $(C_4H_3NO_2){:}CHC_6H_5$, m.p. 141° (*Schiff*, *Betti*, Ber. **30,** 1337). 3-**Phenyl-5-isoxazolone,** m.p. 152°; silver salt, $C_9H_6NO_2Ag$; aniline salt, m.p. 111°; methyl derivative, $C_9H_6NO_2{\cdot}CH_3$, m.p. 78°. When treated with benzoyl chloride and alkali phenylisoxazolone yields 2 isomeric alkali-insoluble benzoyl esters, m.p. 161° and 115° (*Rabe*, Ber. **30,** 1614). 4-**Benzylidene-3-phenyl-5-isoxazolone,** m.p. 191° (*Wahl*, *Meyer*, C.r. 146, 638). 3,4-**Dimethyl-5-isoxazolone,** m.p. 124°; 3-**methyl-4-ethyl-5-isoxazolone,** m.p. 50° (*Uhlenhuth*, Ann. **296,** 56); 3-**methyl-4-benzyl-5-isoxazolone,** m.p. 106° (*Schiff*, *Viciani*, Ber. **30,** 1161). 3-**Phenyl-5-iminoisoxazolone,** $O{-}N{=}C(C_6H_5){-}CH_2{-}C{:}NH$, m.p. 111°, is prepared from benzoylacetonitrile, $C_6H_5{\cdot}CO{\cdot}CH_2{\cdot}CN$, or benzoacetodinitrile and hydroxylamine (*Rothenburg*, Ber. **27,** 1095; *Burns*, J.pr. **47,** 124).

3-**Phenyl-5-benzoyl-4-isoxazolone,** $O{\cdot}N{:}C(C_6H_5){\cdot}CO{\cdot}CH{\cdot}COC_6H_5$, m.p. 175°, is obtained from benzoylformoin (p. 119) and hydroxylamine (*Abenius*, *Söderbaum*, Ber. **25,** 3468; *cf.* *Scholl*, Ber. **30,** 1290).

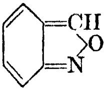
Metafulminuric acid, 4,5-**diisonitrosoisoxazoline,** $O{\cdot}N{:}CH{\cdot}C({:}NOH){\cdot}C{:}NOH$, detonating at 106°, is a derivative of 4,5-isoxazolinedione. It is formed by the spontaneous polymerization of fulminic acid. When warmed with water, or more rapidly when treated with alkali, it rearranges to α,β-diisonitrosohydracrylonitrile, $CN{\cdot}C({:}NOH){\cdot}C({:}NOH)OH$ (*Wieland*, *Hess*, Ber. **42,** 1346). 3-**Amino-4-isonitroso-5-isoxazolone,** $O{\cdot}N{:}C(NH_2){\cdot}C({:}NOH){\cdot}CO$, m.p. 160° (dec.) (*Wieland*, *Gmelin*, Ann. **367,** 83).

5-**Isoxazolone-4-carboxylic acid ester,** $O{\cdot}N{:}CH{\cdot}CH(CO_2C_2H_5)CO$, is obtained from ethoxymethylenemalonic acid ester or propylene-α,α,γ,γ-tetracarboxylic acid ester with hydroxylamine; when its silver salt is heated with methyl iodide, an N-methyl derivative, $O{\cdot}N(CH_3){\cdot}CH{:}C(CO_2C_2H_5)CO$, is formed (*Claisen*, Ann. **297,** 81; Ber. **30,** 1480).

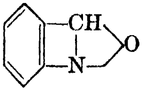
The following structures are possible for bicyclic ring systems containing a benzene and an isoxazole ring sharing two adjacent carbon atoms:



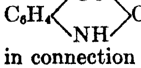
1,2-Benzisoxazole,
Indoxazene



or



Anthranil or β,γ-Benzisoxazole

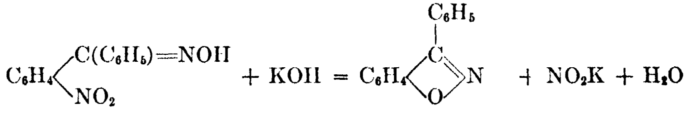
Of these, anthranil has already been treated in Volume III, p. 278; benzisoxazolone, 

$$C_6H_4{<}\begin{matrix}CO\\NH\end{matrix}{>}O$$

the anhydride of *o*-hydroxylaminobenzoic acid, is described in connection with the acid.

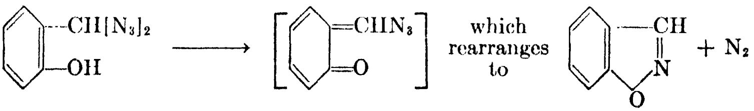
4. BENZISOXAZOLES

Benzisoxazoles or indoxazenes are prepared: (*1*) From the oximes of *o*-halogeno- or *o*-nitrobenzophenone with alkali, and from *o*-aminobenzophenone with nitrous acid (Vol. III, p. 518; *Cathcart, Meyer*, Ber. **25**, 1498; *Meyenburg*, Ber. **26**, 1657) (*cf.* method *3a* for the preparation of 1-alkylindazoles, p. 115); this reaction depends on the spacial configuration of the oximes (*Meisenheimer, Zimmermann, v. Kummer*, Ann. **446**, 205):



A similar synthesis of benzisoxazoles consists in heating the monoacetyl derivatives of the oximes of *o*-hydroxyaryl aldehydes or ketones in a vacuum (*Lindemann, Thiele*, Ann. **449**, 63).

(*2*) α-Triazo-*o*-cresols are converted to benzisoxazoles by warming in solution. This reaction apparently takes the following course (*Lindemann, Mühlhaus*, Ann. **446**, 1):



Properties.—Benzisoxazoles having free 3-positions rearrange in the presence of alkali to salicylic acid nitriles, a reaction similar to that given by the monocyclic isoxazoles (p. 119). For the influence of substituents in the 3-position on the fission of the ring, see *Lindemann, Cissée*, Ann. **469**, 44; for the influence of substituents in the benzene ring, see *Lindemann, Romanoff*, J.pr. **122**, 230.

1,2-Benzisoxazole, *indoxazene*, b.p. 84° (11 mm.), d 1.170 (*Lindemann, Thiele*, Ann. **449**, 63; *v. Auwers*, Ber. **57**, 461), from the oxime obtained from salicylaldehyde and N-hydroxyurea or from the monoacetate of salicylaldoxime by heating in a vacuum. In aqueous sodium hydroxide it rearranges to salicylic acid nitrile. **3-Methyl-1,2-benzisoxazole**, b.p. 92.5° (11 mm.); **3,5-dimethyl-1,2-benzisoxazole**, b.p. 116° (13 mm.) (*Lindemann, Cissée*, Ann. **449**, 63).

Phenylbenzisoxazole, $C_{13}H_9NO$, m.p. 84°, b.p. 331–336°, is converted to a dinitro derivative by fuming nitric acid. When reduced with sodium and alcohol it opens to α-phenyl-*o*-hydroxybenzylamine, $C_6H_4\begin{array}{l}\diagup CH(C_6H_5)NH_2\\ \diagdown OH\end{array}$; with HI and phosphorus it gives *o*-hydroxybenzophenone (*Cohn*, Mo. **16**, 267; **17**, 1020). For other benzisoxazole derivatives, see *Lindemann, Könitzer, Romanoff*, Ann. **456**, 290.

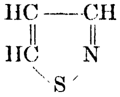
3-Amino-6-nitrobenzisoxazole, m.p. 234°, from the 3-carboxylic acid azide (*Lindemann, Cissée*, Ann. **469**, 55), can be converted to **3-hydroxy-6-nitrobenzisoxazole**, m.p. 88°, by diazotization.

Naphth[1,2-*d*]isoxazole, m.p. 83° (*Lindemann, Könitzer, Romanoff*, Ann. **456**, 293). **6-Anthr[9,1]isoxazol-6-one**, $\begin{array}{l}O\cdot C_6H_3\cdot C{=\!=}N\\ |\qquad |\qquad\ \ |\qquad |\\ N{:}C{-\!-}C_6H_3\cdot O\end{array}$, and **anthra[9,1-*cd*,10,5-*c'*,*d'*]diisoxazole**, $\begin{array}{l}C_6H_4\cdot C{=\!=}N\\ |\qquad\ \ |\qquad |\\ CO{-}C_6H_3\cdot O\end{array}$ (*Freund, Achenbach*, Ber. **43**, 3251). For dyes from dioxoanthraisoxazoles, see Ger. Pat. 343252, 1915, Frdl. **XIII**, 404; Ger. Pat. 360422, 1918, Frdl. **XIV**, 860.

4,5,6,7-Tetrahydrobenzisoxazoles are obtained from hydroxymethylenecyclohexanones and hydroxylamine (*v. Auwers, Bahr, Frese*, Ann. **441**, 54).

5. ISOTHIAZOLES

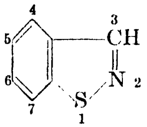
Isothiazole (I) is the sulfur analogue of isoxazole. No member of this group is known. A necessary condition for the development of this field is the preparation

(I)


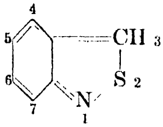
of the unknown thiohydroxylamine, $HS \cdot NH_2$.

6. BENZISOTHIAZOLES

As in the corresponding ring systems containing oxygen (p. 122) there are two possible isomeric benzisothiazoles:

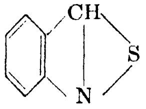


1,2-Benzisothiazole



2,1-Benzisothiazole

or

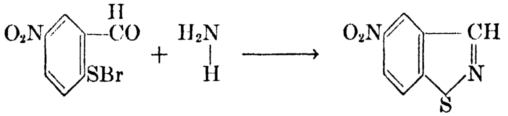


Thioanthranil.

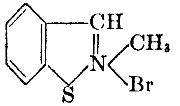
Both parent compounds and derivatives of them are known.

1,2-Benzisothiazoles

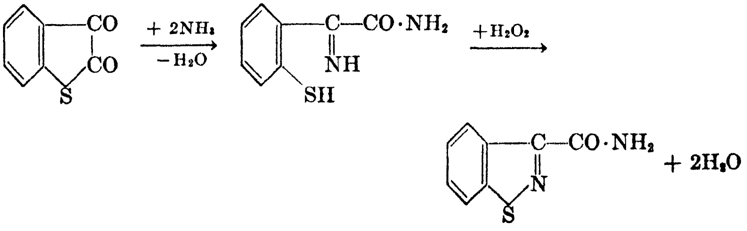
Derivatives of this ring system are obtained: *(1)* By the action of ammonia on aryl sulfur halides which contain a CO-group in an *o*-position to the S-atom (*Fries, Brothuhn*, Ber. **56**, 1630):



When these same aryl sulfur halides are treated with primary amines, compounds having a salt-like character are formed which are apparently benzisothiazolium derivatives:

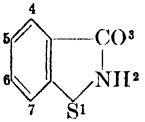


(2) By oxidation of thianaphthenequinones with H_2O_2 in the presence of ammonia (*Stollé*, Ber. **58**, 2095):

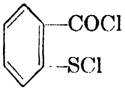


1,2-Benzisothiazole, m.p. 37°, b.p. 220° (*Stollé*, Ber. **58**, 2096). **3-Amino-1,2-benzisothiazole**, m.p. 115°, from the carboxylic acid azide by the Curtius method (*Stollé*, Ber. **58**, 2098). **5-Nitro-1,2-benzisothiazole**, m.p. 153° (*Fries*, Ann. **454**, 279). **3-Phenyl-5-nitro-1,2-benzisothiazole**, m.p. 124° (*Fries*, Ann. **454**, 290). **3-Phenyl-5-amino-1,2-benzisothiazole**, m.p. 131°. **Benzisothiazole-3-carboxylic acid** (*Stollé*, Ber. **58**, 2098). Naphthisothiazoles are also obtained by method *2* (*Stollé*, *Badstübner*, J.pr. **121**, 266).

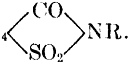
3(2)-**Benzisothiazolone** (I) is a derivative of 2,3-dihydro-1,2-benzisothiazole. It and its derivatives are prepared from compounds of type II by reaction with



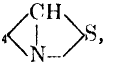
(I)



(II)

ammonia (*McClelland*, *Gait*, J. **1926**, 921; *Reissert*, *Manns*, Ber. **61**, 1308). Oxidation with H_2O_2 converts them to saccharines,  $C_6H_4\left\langle\begin{matrix}CO\\SO_2\end{matrix}\right\rangle NR$.

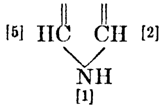
3(2)-**Benzisothiazolone**, m.p. 155°; **2-methyl-3-benzisothiazolone**, m.p. 51°; **2-phenyl-3-benzisothiazolone**, m.p. 140°.

2,1-Benzisothiazole, *thioanthranil*  $C_6H_4\left\langle\begin{matrix}CH\\|\\N\end{matrix}\right\rangle S$, b.p. 242° (448 mm.), is formed by reduction of the *o*-nitrobenzyl ester of thiocarbamic acid or of *o*-nitrobenzylthiol; when heated with phenylhydrazine or hydrazine hydrate it gives the phenylhydrazone or the azine of *o*-aminobenzaldehyde (*Gabriel*, *Leupold*, Ber. **31**, 2185).

7. IMIDAZOLES

This group of compounds and the following groups of oxazoles and thiazoles can be considered as cyclic amidines, imino ethers, and thioimino ethers of carboxylic acids; these relationships are apparent in their syntheses.

IMIDAZOLE, glyoxaline, 1,3-*diazole:*

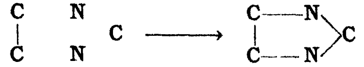


is isomeric with pyrazole. Like the pyrimidines, the imidazoles are cyclic amidines. *Allantoin* (Vol. I, p. 627), an imidazole derivative, has been known since 1799, when it was discovered in the allantoic fluid of cows. Another physiologically important derivative of imidazole is histidine, a fission product of proteins.

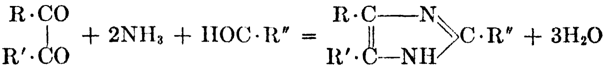
History.—Imidazole was discovered by *Debus* in 1856 as a product of the reaction of glyoxal and ammonia, a reaction which was clarified by *Radziszewski* in 1882 and generalized for other ketones. The peculiar bases prepared by *Wallach* in 1876 from dialkyloximide chlorides, which he called *oxalines*, were later found to be imidazoles. In 1882 *Japp* postulated, on the basis of the relation between lophines and imidazoles, the structural formula for imidazole which is now generally accepted; it has been verified by the more recent syntheses of *Wohl* and *Marckwald* and of *Bamberger*. The name imidazole, which was given to the ring system by *Hantzsch* (Ann. **249**, 2), is now used almost exclusively.

Syntheses of Imidazole and Its Derivatives

I. Of the type:



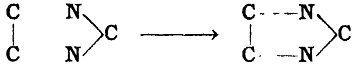
This type includes the condensation of glyoxal and other *o*-dioxo compounds with NH_3 and aldehydes (*Radziszewski*, Ber. **15**, 2706):



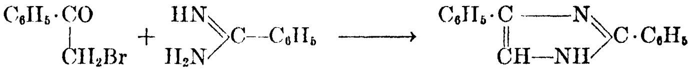
Ammonia and glyoxal alone form imidazole, due to the partial decomposition of glyoxal into formaldehyde and formic acid.

Other examples are the preparations of imidazoles from 1,2-diketones and amines of the formula $RCH_2 \cdot NH_2$; benzil and benzylamine give *triphenyl*-1-*benzylimidazole*, and benzil and ethylamine give *diphenyl*-2-*methyl*-1-*ethylimidazole* (*Japp, Davidson*, J. **1895**, 1, 32).

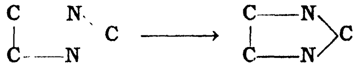
II. Of the type:



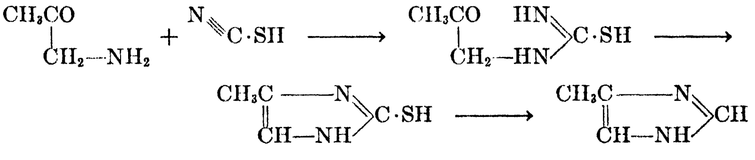
Imidazoles are prepared from carboxylic acid amidines with α-halogeno ketones or α-oxo alcohols (*Knuckell*, Ber. **34**, 637); see the syntheses of oxazoles and thiazoles (pp. 136 and 140):



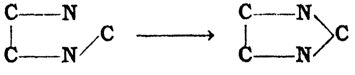
III. Of the type:



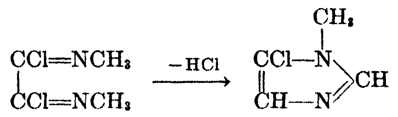
This synthesis introduced by *Wohl* and *Marckwald* consists in the reaction of amino aldehydes or amino ketones or their acetals with potassium thiocyanate to form substituted thioureas, which are condensed by hydrochloric or sulfuric acid to 2-imidazolethiols, which lose sulfur on oxidation (*Wohl, Marckwald*, Ber. **22**, 1353; *Marckwald*, Ber. **25**, 2354; *Gabriel, Pinkus*, Ber. **26**, 2204; *Basse, Klinger*, Ber. **31**, 1220):



IV. Of the type:

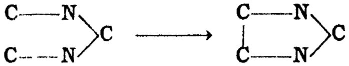


By an unusual reaction the alkylimide chlorides of oxalic acid give chlorine substitution products of imidazoles, which can be reduced to imidazoles (*Wallach*, Ann. **214**, 278):

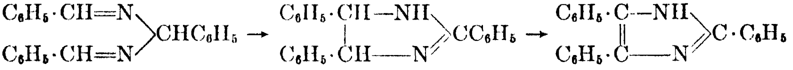


Dimethyloxalimide chloride **1-Methyl-5-chloroimidazole**

V. Of the type:

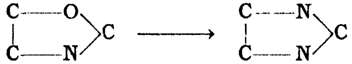


Hydrobenzamide (Vol. III, p. 272) and similar aromatic amines rearrange when heated to triaryldihydroimidazoles, which readily lose 2H to form triarylimidazoles:



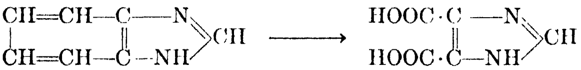
Hydrobenzamide Amarine Lophine

VI. Of the type:

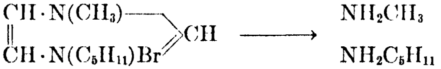


Several imidazoles have been obtained from the corresponding oxazoles (p. 137) by heating with ammonia (*Minovici*, Ber. **29**, 2098).

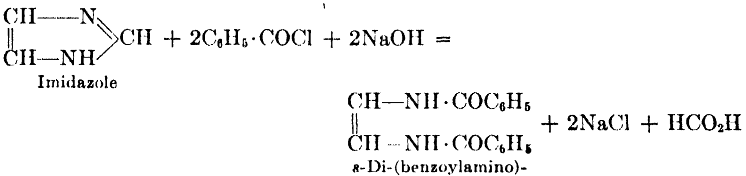
VII. A theoretically important method is the synthesis of imidazoledicarboxylic acids from benzimidazole (p. 133) by oxidation with permanganate (*Bamberger, Berlé*, Ann. **273**, 339):



Properties.—The imidazoles are more basic than the isomeric pyrazoles (*Dedichen*, Ber. **39**, 1831). The imine hydrogen can be replaced by metals, especially silver, and by alkyl groups by means of alkyl iodides, dimethyl sulfate, or diazomethane (*Forsyth, Pyman*, J. **127**, (1925) 573). The tertiary bases add alkyl halides energetically; the non-alkylated N-atom must take part in this reaction, since the addition products decompose when boiled with aqueous potassium hydroxide into two primary amines, for example:



(*Pinner, Schwarz*, Ber. **35**, 2457). When heated, 1-alkylimidazoles rearrange, the alkyl group wandering to the 2-C atom. Acyl groups are introduced with difficulty and are readily split off. Benzoyl chloride in sodium hydroxide solution or pyridine attacks imidazole and the simpler imidazole derivatives with free imine groups (*Fischer*, Ber. **34**, 932; *Pinner, Schwarz*, Ber. **35**, 2448; *Windaus, Dörries, Jensen*, Ber. **54**, 2745) even at 0°, forming a carboxylic acid and a dibenzoyldiamine. Isovaleryl chloride acts similarly.

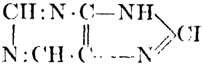


Imidazole

s-Di-(benzoylamino)-ethylene

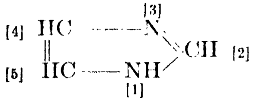
Conversely, the di-(acylamino)ethylenes are converted to imidazoles when heated with acid anhydrides (*Windaus, Langenbeck*, Ber. **55**, 3706).

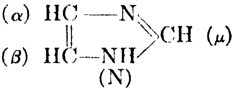
The imidazoles are very stable toward reducing agents and toward oxidizing agents. They are attacked slightly by chromic acid, more energetically by potassium permanganate (*Pinner, Schwarz*, Ber. **35**, 2448); hydrogen peroxide forms oxamines. Imidazoles with free imine groups couple with aromatic diazo compounds; the products are not diazoamino derivatives, as might be assumed, but C-azo derivatives which have the azo group in the 2- or the 4(5)-position (*Fargher, Pyman*, J. **115**, 217). The purines (Vol. I, p. 638), which contain a con-

densed imidazole ring, 

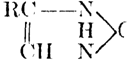
behave similarly.

The position of the substituents in imidazole, which is now indicated by numbers (I) was formerly shown by symbols (II).

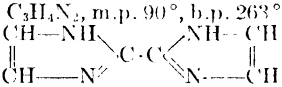
(I)




(II)

The hydrogen atoms in the 4- and 5-positions are equivalent, which is expressed in this manner of formulating alkylimidazoles: 

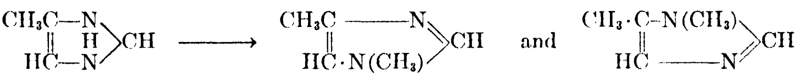
(*cf.* 4-methyl-5-phenylimidazole, see below).

IMIDAZOLE, glyoxaline, $C_3H_4N_2$, m.p. 90°, b.p. 263°, is formed together with *glycosine* (2,2′-**biimidazole**, 

, *Lehmstedt*, Ann. **456**, 253) from glyoxal and ammonia, advantageously with the addition of formaldehyde (*Behrend, Schmitz*, Ann. **277**, 336); it is also prepared from 2-imidazolethiol and from its dicarboxylic acid (see above). It is soluble in alcohol, ether, and water; the solutions when treated with alkali phosphoresce in the air (*cf.* lophine). It forms salts with all acids except carbonic acid. Silver nitrate precipitates the *silver salt* of *imidazole*, $C_3H_3N_2Ag$; methyl iodide forms **1-methylimidazole**, m.p. −6°, b.p. 199°, d 1.0363, which is also obtained from dimethyloxalimide chloride by method *IV* (p. 125). The alkaloid pilocarpine is a derivative of 1-methylimidazole. **1-Phenylimidazole**, m.p. 13°, b.p. 276°, is formed from its mercaptan according to method *III* (p. **125**).

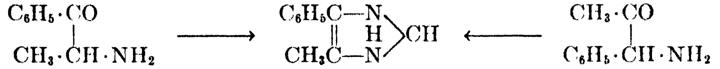
2-Methylimidazole, m.p. 137°, b.p. 267°, is prepared by rearrangement of 1-methylimidazole (see above) or from glyoxal, acetaldehyde and NH_3; with ethyl iodide it forms **1-ethyl-2-methylimidazole**, b.p. 213°, which is also obtained from diethyloxalimide chloride and which possesses a physiological action similar to *atropine*. **2-Ethylimidazole**, m.p. 80°, b.p. 268°.

4(5)-Methylimidazole, m.p. 56°, b.p. 263°, from its mercaptan by method *III* (p. 125) (*Gabriel, Pinkus*, Ber. **26**, 2204), and from grape sugar and other hexoses and pentoses by treatment with zinc hydroxide-ammonia (*Windaus, Knoop*, Ber. **38**, 1166; *Windaus*, Ber. **40**, 799; Vol. I, p. 696). Methylation of methylimidazole with dimethyl sulfate and alkali produces both 1,4- and 1,5-**dimethylimidazole**, b.p. 199° and 224°:



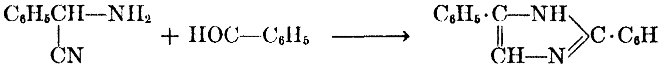
In this reaction the methylimidazole behaves as a mixture of 4- and 5-methylimidazole (*Pyman*, J. **97**, 1814).

2,4,5-Trimethylimidazole, m.p. 183°, b.p. 271°, from biacetyl, NH_3, and aldehyde. **4(5)-Phenylimidazole**, m.p. 129°, from phenylglyoxal, NH_3, and formaldehyde; with NH_3 alone phenylglyoxal gives a mixture of products, including 2-benzoyl-4-phenylimidazole, m.p. 280° (*Pinner*, Ber. **38**, 1531). **4-Methyl-5-phenylimidazole**, m.p. 185°, is obtained from methylphenylimidazolethiol prepared according to method *III* (p. **125**) by oxidation with HNO_3; the same methylphenylimidazole results whether α-aminopropiophenone (I) or the isomeric α-acetylbenzylamine (II) is used as the starting material:

(I)


(II)

This also demonstrates the equivalence of the 4- and 5-positions of imidazole (*Gabriel*, Ber. **41**, 1926); *cf.* 2,5-dimethylbenzimidazole (p. 133), 3-methylpyrazole (p. 93), and Vol. I. **2,4-Diphenylimidazole**, m.p. 193°, from benzamidine and phenacyl bromide (*Knuckell*, Ber. **34**, 639). **4,5-Diphenylimidazole**, m.p. 227°, from benzil, formaldehyde, and NH_3, together with 2,4,5-triphenyloxazole (p. 137), benzilamide and imabenzil (*Pinner*, Ber. **35**, 4136; **38**, 1536). 2,5-**Diphenylimidazole,** m.p. 162°, is obtained from 2,5-diphenyloxazole (p. 137) with alcoholic NH_3 at 300°, and by the condensation of α-aminophenylacetonitrile and benzaldehyde with HCl (*cf.* method *4* for the oxazoles, p. 136) (*Minovici*, Ber. 29, 2103):



Lophine, 2,4,5-**triphenylimidazole**, m.p. 275°, is prepared: (*1*) from benzil, benzaldehyde, and NH_3; (*2*) from hydrobenzamide by heating (*Pinner*, Ber. **35**, 4140) or from amarine by oxidation; (*3*) from 2,4,6-triphenyl-*s*-triazine or triphenyltricyanogen by reduction accompanied by elimination of NH_3; and (*4*) from benzamidine and benzoin (*Kulisch*, Mo. **17**, 300). Lophine (from λόφος, tuft of feathers, referring to its tufted crystalline form) phosphoresces strongly when shaken with alcoholic potassium hydroxide, decomposing into NH_3 and benzoic acid.

Halogen derivatives of imidazoles are formed by substitution. 2-**Bromoimidazole** is obtained in good yield by the action of cyanogen bromide (*Langenbeck*, J.pr. **119**, 77). 5-**Chloroimidazoles** are prepared from the dialkyloxalimide chlorides (p. 125). **Tribromoimidazole**, $C_3Br_3N_2H$, m.p. 214°, from imidazole and bromine; 2,4,5-**triiodoimidazole**, $C_3I_3N_2H$, m.p. 192°, and 1,2,4,5-**tetraiodoimidazole**, $C_3I_4N_2$, dec. 160°, from imidazole and iodine (*Pauly*, Ber. **43**, 2243); **5-chloro-1-methylimidazole**, $C_3H_2ClN_2 \cdot CH_3$, b.p. 205°, and **5-chloro-1,2-dimethylimidazole**, $C_3HCl(CH_3)N_2 \cdot CH_3$, b.p. 218°, from dimethyl- and ethylmethyloxalimide chloride.

Nitro derivatives of the imidazoles are obtained by the action of nitric acid-sulfuric acid or fuming nitric acid on imidazoles. The nitro group apparently enters in the 4(5)-position. The nitroimidazoles with a free imine group dissolve in alkali to yellow solutions. 4-**Nitro-5-methylimidazole**, m.p. 248°; **5-nitro-2,4-dimethylimidazole**, m.p. 252°; 4-**nitro-1,5-dimethylimidazole**, m.p. 161° (*Windaus*, Ber. **42**, 761).

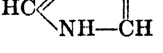
Nitroimidazoles reduce to aminoimidazoles. Derivatives with an amino group in a side-chain are formed from carboxylic acid azides by the Curtius reaction or, synthetically, by method *III* (p. 125). 4(5)-**Aminomethylimidazole dihydrochloride** sinters at 236° (*Windaus, Opitz*, Ber. **44**, 1722). For **histamine, 4-imidazoleëthylamine**, see p. 129.

Mercaptans are obtained by condensation of dialkoxyethyl- or acetonylthiourea or similar substances (p. 125). 2-**Imidazolethiol**, m.p. 222° (dec.), reacts with methyl iodide to give the methyl ether, $C_3H_3(SCH_3)N_2$, m.p. 139° (*Marckwald*, Ber. **25**, 2359). 4,5-**Diphenyl-2-imidazolethiol**, $C_3(C_6H_5)_2NH_2(SH)$, is prepared from benzoin and thiourea (*Anschütz*, Ann. **284**, 8; *cf. Basse, Klinger*, Ber. **31**, 1220). 4(5)-**Aminomethyl-2-imidazolethiol**, $C_3(CH_2NH_2)H_2N_2(SH)$, m.p. 188°, from acetonediamine hydrochloride and potassium thiocyanate, is converted by treatment with dilute nitric acid into 4(5)-**hydroxymethylimidazole**, $C_3(CH_2OH)$-H_3N_2, m.p. 94° (*Pyman*, J. 99, 668).

4(5)-**Sulfonic acids** of imidazole result from direct sulfonation (*Barnes, Pyman*, J. **1927**, 2711); 2-sulfonic acids are obtained by oxidation of the corresponding 2-imidazolethiols (see p. 125, method *III*) with hydrogen peroxide.

4,5-**Imidazoledicarboxylic acid**, $C_3H_2(COOH)_2N_2$, from dihydroxytartaric acid, NH_3, and formaldehyde [*Maquenne*, Ann.chim.phys. **24** (1891), 525], and by oxidation of benzimidazole (*Bamberger, Berlé*, Ann. **273**, 339), decomposes immediately when heated into CO_2 and imidazole. The dicarboxylic acid is useful for the isolation of a number of bases whose acid salts are generally sparingly soluble in water (*Pauly, Ludwig*, Z.physiol.Chem. **121**, 165). For the synthesis of a series of 2-alkylimidazoledicarboxylic acids, see *Yllner*, Arkiv Kemi, Miner. Geol. **9** (1927), No. 41, 1.

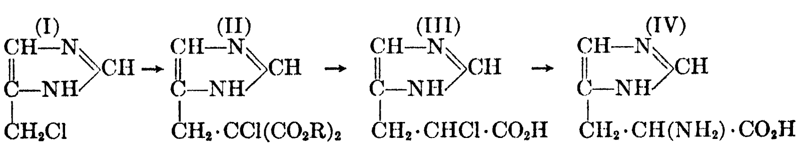
l-**HISTIDINE,** *α-amino-4(5)-imidazolepropionic acid:*



(*Pauly*, Z.physiol.Chem. **42**, 508), flaky crystals, m.p. 285° (dec.), $[\alpha]^{20}_{D}$ −39.74 (*Abderhalden*, *Weil*, Z.physiol.Chem. **77**, 438), was discovered by *A. Kossel* in 1896 (Sitzber.kgl.preuss.Akad.Wiss., April 9) among the disintegration products of the protamine sturin; it is formed in the hydrolysis of many proteins, especially hemoglobin [preparation from blood corpuscles, *Jones*, J.Biol.Chem. **33** (1919), 429; *Hanke*, *Koessler*, *ibid.*, **43** (1921), 521]. The *levo* configuration of the asymmetric carbon atom was determined by degradation to *l-aspartic acid* (*Langenbeck*, Ber. **58**, 227; Vol. I, p. 608). *Monohydrochloride*, plates (from water), m.p. 255°. *Methyl ester dihydrochloride*, m.p. 196°. Histidine forms a molecular compound (1:1), m.p. 224–226°, with *flavianic acid* (naphthol yellow S) which is sparingly soluble in dilute mineral acids (*Kossel*, *Gross*, Z.physiol.Chem. **135**, 168). Like other imidazoles, histidine couples in solutions made alkaline with soda with diazobenzenesulfonic acid to form a red azo dye. Of the other decomposition products of proteins, only tyrosine gives this reaction (*Pauly*, Z. physiol.Chem. **42**, 513). Another characteristic property is the formation of a sparingly soluble acid salt with 4,5-imidazoledicarboxylic acid, m.p. 254° (*Pauly*, *Ludwig*, Z.physiol.Chem. **121**, 168). Color reaction of histidine when warmed with bromine [*Knoop*, Beitr.chem.Physiol.Path. **11** (1908), 356; *Hunter*, Biochem.J. **16** (1923), 637].

When treated with HNO_2 histidine is converted to **α-hydroxyimidazolepropionic acid, *l*-imidazolelactic acid,** $C_3H_3N_2CH_2CH(OH)COOH + H_2O$, m.p. 204° (dec.), which can be broken down to **imidazoleacetic acid,** $C_3H_3N_2CH_2COOH + H_2O$, m.p. 220° (dec.), **imidazolecarboxylic acid,** $C_3H_3N_2COOH$, m.p. 286° (dec.), and finally to imidazole itself [*Knoop*, Beitr.chem.Physiol.Path. **10** (1907), 111]. When the α-hydroxyimidazolepropionic acid is reduced with HI and P, it yields **imidazolepropionic acid,** $C_3H_3N_2CH_2CH_2COOH$, m.p. 209°. Histidine hydrochloride can be transformed by the action of bacteria to *d-imidazolelactic acid*, m.p. 196°, α_D +33.7° [*Hirai*, Acta Schol.Med.Univ.Imp.Kioto **2** (1918), 447]; *Bacillus coli* under certain conditions gives imidazolepropionic acid [*Koessler*, *Hanke*, J.Biol.Chem. **39** (1920), 539]. This acid can be synthesized by condensation of glyoxylpropionic acid, $CHO\cdot CO\cdot CH_2\cdot CH_2\cdot COOH$ (Vol. I, p. 601), with ammonia and formaldehyde according to method *I* (p. **125**) [*Knoop*, *Windaus*, Beitr.chem.Physiol.Path. **7** (1905), 144]; its azide can be converted by the Curtius reaction to 4-**imidazoleëthylamine, histamine,** $C_3H_3N_2\cdot CH_2\cdot CH_2NH_2$, m.p. 83–84°, picrate m.p. 234° (dec.) (*Windaus*, *Vogt*, Ber. **40**, 3691). Histamine is also obtained from histidine by heating alone, or, better, with concentrated HCl to 270° (*Ewins*, *Pyman*, J. **99**, 339), or by bacterial disintegration (*Ackermann*, Z.physiol.Chem. **65**, 504). Histamine is found among the alkaloids of ergot, and is often used as a substitute for ergot preparations in gynecology (*Barger*, *Dale*, J. **97**, 2592). For other syntheses of histamine, see *Pyman*, J. **99**, 668, and *Koessler*, *Hanke*, Am. **40**, 1716. The violet coloration which histidine gives with small quantities of cobalt nitrate on addition of alkali is specific for this base and is used for its detection (*Zimmermann*, Z.physiol.Chem. **186**, 260).

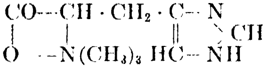
Synthesis of histidine (*Pyman*, J. **99**, 1386). 4(5)-Chloromethylimidazole (I), from 4(5)-hydroxymethylimidazole (p. 128) and PCl_5, when treated with sodium chloromalonic ester yields 4(5)-imidazolechloromalonic ester (II), which saponifies to 4(5)-imidazolechloropropionic acid (III); this reacts with NH_3 to give [*d* + *l*]-histidine, which can be resolved to its optically active components with tartaric acid:



For the quantitative determination of histidine by titration with standardized silver nitrate solution or diazobenzenesulfonic acid, see *Lautenschläger*, Z.physiol. Chem. **102**, 226.

For the preparation of histidine-peptides, see *Bergmann*, *Zervas*, Z.physiol. Chem. **175**, 154.

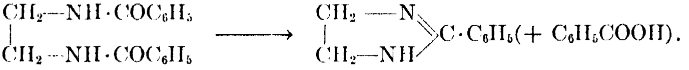
Herzynine is the trimethylbetaine of histidine:



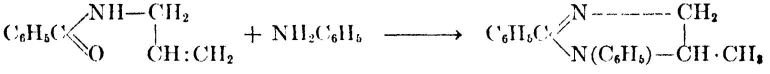
It is found in extracts of various fungi [*Kutscher*, Zentr.Physiol. **24** (1911), 775].

Carnosine, a derivative of histidine in which the NH_2-group is substituted by a β-aminopropionic acid residue, $-CO \cdot CH_2 \cdot CH_2 \cdot NH_2$, is obtained by extraction of muscular substance (*Fürth, Hryntschak*, Biochem.Z. **64** (1916), 172).

HYDROIMIDAZOLES. Imidazoles cannot be reduced to hydro derivatives. Dihydroimidazoles or imidazolines are obtained: (*1*) From acyl derivatives of ethylenediamine and its homologues:

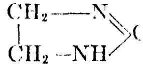


(*2*) The products of the reaction of N-allylacetamide and N-allylbenzamide with the hydrochlorides of aromatic bases are apparently dihydroimidazoles (*Clayton*, Ber. **28**, 1665):



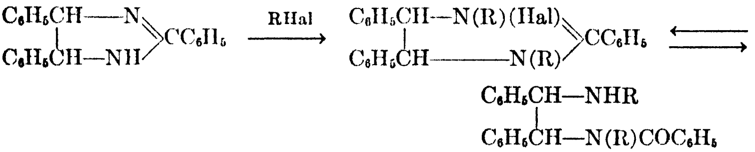
N-Allylbenzamide

1,2-Diphenyl-5-methylimidazoline

2-Methylimidazoline, *lysidine*,  m.p. 105°, b.p. 195–198°, is prepared by heating ethylenediamine hydrochloride with sodium acetate; it forms a very soluble *uric acid salt* (*Ladenburg*, Ber. **27**, 2952). The homologous imidazolines, such as **2-ethyl-, 2,4**(or 2,5)**-dimethyl-,** and **4**(5)**-methyl-2-ethylimidazoline,** behave similarly (*Klingenstein*, Ber. **28**, 1173; *Baumann*, Ber. **28**, 1176). Benzoyl chloride and alkali split methylimidazoline to acetyldibenzoylethylenediamine (*Ladenburg*, Ber. **28**, 3068).

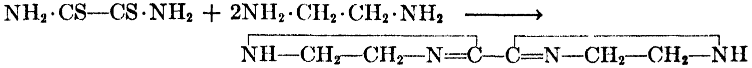
2-Phenylimidazoline, *ethylenebenzamidine*, $C_3H_5(C_6H_5)N_2$, m.p. 101°, is formed from ethylenediamine and thiobenzamide (*Forssel*, Ber. **25**, 2135).

2,4,5-Triphenylimidazoline, amarine, $C_{21}H_{18}N_2$, m.p. 133° (anhydrous), is formed by rearrangement of hydrobenzamide. With alkyl halides it gives dialkyltriphenylimidazolium halides, which are split by alkali to diphenylethylenediamine derivatives, whose hydrochlorides are condensed by heat to the same imidazolium compounds:



The reaction of benzoyl chloride with amarine takes a similar course. When amarine is heated with sodium ethylate at 150–160°, or amarine hydrochloride is heated at 340°, an isomeric **isoamarine,** m.p. 198°, is obtained; the same compound is synthesized from *rac*-dibenzoyldiphenylethylenediamine (Vol. III). It stands in the same relation to amarine as *rac*-tartaric acid does to *meso*-tartaric acid, and can be resolved into optically active components [*Japp, Moir*, Proc. Chem.Soc., **15** (1900), 227; J. **77**, 608]. When oxidized, amarine is converted to lophine (p. 128). **Trifurylimidazoline,** *furfurin* (p. 19) has an analogous composition.

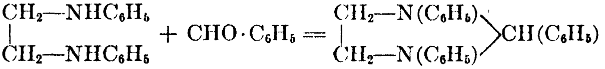
Biimidazoline, $(C_3H_5N_2)_2$, m.p. 290–300°, is the condensation product of thiooxalic acid diamide and ethylenediamine (*Forssell*, Ber. **24**, 1846):



$NH_2\cdot CS—CS\cdot NH_2 + 2NH_2\cdot CH_2\cdot CH_2\cdot NH_2 \longrightarrow$

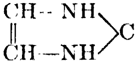
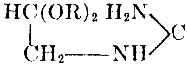
$\overline{NH—CH_2—CH_2—N=C}—\overline{C=N—CH_2—CH_2—NH}$

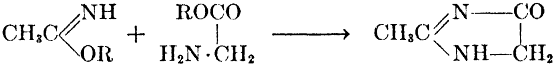
TETRAHYDROIMIDAZOLES, such as **triphenyltetrahydroimidazole,** m.p. 137°, are prepared from N,N′-diphenylethylenediamine and aldehydes (*Moos*, Ber. **20**, 732):



$\begin{array}{l}CH_2—NHC_6H_5\\ |\\ CH_2—NHC_6H_5\end{array} + CHO\cdot C_6H_5 = \begin{array}{l}CH_2—N(C_6H_5)\\ |\\ CH_2—N(C_6H_5)\end{array}\!\!>CH(C_6H_5)$

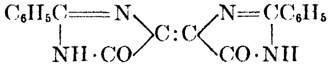
The group comprising the oxo-, thio-, and iminohydroimidazoles includes a series of cyclic urea, thiourea and guanidine derivatives, most of which have been described with the aliphatic compounds.

1. **OXOIMIDAZOLINES,** imidazolones, or ureins are formed from α-ureido-keto compounds by inner condensation: **2-Imidazolone,**  $\begin{array}{l}CH—NH\\ \|\\ CH—NH\end{array}\!\!>CO$, m.p. 105°, from β-dialkoxyethylurea,  $\begin{array}{l}HC(OR)_2\ H_2N\\ |\\ CH_2——NH\end{array}\!\!>CO$ (*cf.* Vol. I); various imidazolones have been prepared from benzoin and benzil with ureas (*cf. Marckwald*, Ber. **25**, 2357; *Gabriel, Posner*, Ber. **27**, 1038, 1144; *Fischer, Hunsalz*, Ber. **27**, 2203; *Magnanini*, Gazz. **19**, 573; *Biltz*, Ann. **368**, 156). **4,5-Diphenyl-2 imidazolone,** m.p. 324° (*Biltz*, Ann. **339**, 249). 4-Imidazolones, such as **2-methyl-4-imidazolone,** m.p. 141°, are obtained by condensation of iminoethers with α-amino fatty acid esters (*Finger*, J.pr. **76**, 93; *Finger, Zeh, ibid.*, **82**, 50):



$CH_3C\begin{array}{l}\diagup NH\\ \diagdown OR\end{array} + \begin{array}{c}ROCO\\ |\\ H_2N\cdot CH_2\end{array} \longrightarrow CH_3C\begin{array}{l}\diagup N——CO\\ \qquad\qquad |\\ \diagdown NH—CH_2\end{array}$

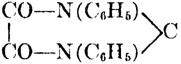
Glyoxaline red, 2,2′-*diphenyl*-4,4′-*bi*-5-*imidazolone*:



$\begin{array}{l}C_6H_5C==N\\ |\\ NH\cdot CO\end{array}\!\!>C:C<\!\!\begin{array}{l}N=CC_6H_5\\ \qquad |\\ CO\cdot NH\end{array}$

ruby crystals, from acetylenedicarboxylic acid ester and 2 mols of benzamidine [*Ruhemann, Stapleton*, Proc. Chem. Soc. **16** (1900), 121].

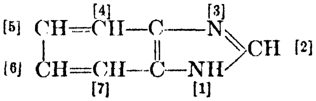
2. **OXO-** and **THIOTETRAHYDROIMIDAZOLES** include the cyclic *alkyleneureas* and *thioureas* (Vol. I).

3. **DIOXO-** and **IMINOÖXOTETRAHYDROIMIDAZOLES** include the *hydantoins* and *glycocyamidines*, such as *hydantoin* and *creatinine* (Vol. I, pp. 49, 514). Other members of this group are **vinylideneoxanilide,**  $\begin{array}{l}CO—N(C_6H_5)\\ |\\ CO—N(C_6H_5)\end{array}\!\!>C:CH_2$, m.p. 209°, and its homologues, which result from condensation of oxanilide with acetic anhydride and sodium acetate or homologous acids (*v. Pechmann, Ansel*, Ber. **33**, 613).

4. **TRIOXO-** and **IMINODIOXOTETRAHYDROIMIDAZOLES** include *oxalylurea* or *parabanic acid* (Vol. I, p. 629) and *oxalylguanidine* (*Traube*, Ber. **26**, 2552).

8. BENZIMIDAZOLES

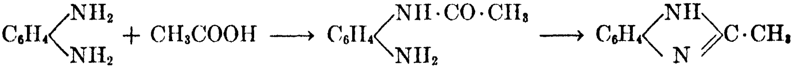
The benzimidazoles, sometimes called cyclic amidines, contain an imidazole ring condensed with a benzene ring:



$\begin{array}{l}\qquad\quad [4]\qquad\qquad [3]\\ [5]\ CH=CH—C——N\\ \quad |\qquad\qquad \|\qquad\quad >CH\ [2]\\ [6]\ CH=CH—C—NH\\ \qquad\quad [7]\qquad\qquad [1]\end{array}$

Their relationship to imidazole is made evident by the formation of imidazoledicarboxylic acid as an oxidation product of benzimidazole (p. 133).

Syntheses. (*1*) By condensation of *o*-phenylenediamines with carboxylic acids or their anhydrides, chlorides, or amides, with elimination of water (*Ladenburg*, Ber. **8,** 677; **11,** 826); acyl compounds are formed as intermediate products:

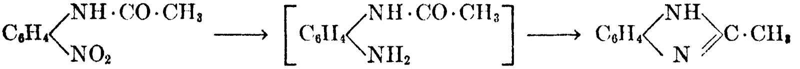


$$C_6H_4\left\langle\begin{matrix}NH_2\\NH_2\end{matrix}\right. + CH_3COOH \longrightarrow C_6H_4\left\langle\begin{matrix}NH\cdot CO\cdot CH_3\\NH_2\end{matrix}\right. \longrightarrow C_6H_4\left\langle\begin{matrix}NH\\N\end{matrix}\right\rangle C\cdot CH_3$$

o-Phenylenediamine — Acetyl-*o*-phenylenediamine — 2-Methylbenzimidazole

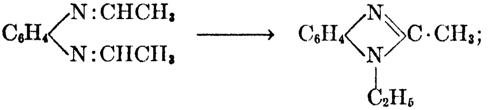
Diacyl-*o*-phenylenediamines also give benzimidazoles (*Bistrzycki*, *Ulffers*, Ber. **23,** 1876; **25,** 1992). The anhydrides of dibasic acids react as monobasic acids; for example, *o*-phenylenediamine and succinic anhydride give *2-benzimidazolepropionic acid* (*Fischer*, Ber. **27,** 2773), and *o*-phenylenediamine and phthalic anhydride give *2-phenylbenzimidazole-o-carboxylic acid* (*Thiele*, *Falk*, Ann. **347,** 116). *o*-Naphthalenediamines and other aromatic 1,2-diamines react in the same way as *o*-phenylenediamine.

(*2*) By reduction of acylated *o*-nitroanilines, acylated *o*-phenylenediamines being formed first (*Hobrecker*, Ber. **5,** 920):

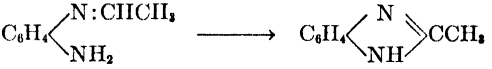


$$C_6H_4\left\langle\begin{matrix}NH\cdot CO\cdot CH_3\\NO_2\end{matrix}\right. \longrightarrow \left[C_6H_4\left\langle\begin{matrix}NH\cdot CO\cdot CH_3\\NH_2\end{matrix}\right.\right] \longrightarrow C_6H_4\left\langle\begin{matrix}NH\\N\end{matrix}\right\rangle C\cdot CH_3$$

(*3*) N-Alkylated benzimidazoles are obtained by the action of aldehydes on *o*-diamines (the *aldehydins* of *Ladenburg*, Ber. **11,** 590). The dialkylidene-*o*-diamines, which are probably the first products of the reaction, rearrange immediately to N-alkylbenzimidazoles (*Hinsberg*, Ber. **20,** 1585); the non-alkylated benzimidazole is formed as a side-product from the monoalkylidene compound:



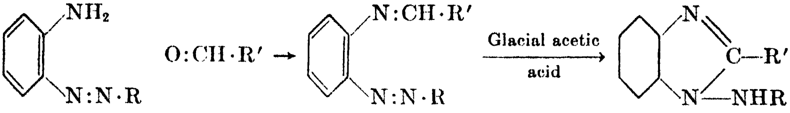
$$C_6H_4\left\langle\begin{matrix}N:CHCH_3\\N:CHCH_3\end{matrix}\right. \longrightarrow C_6H_4\left\langle\begin{matrix}N\\N(C_2H_5)\end{matrix}\right\rangle C\cdot CH_3;$$



$$C_6H_4\left\langle\begin{matrix}N:CHCH_3\\NH_2\end{matrix}\right. \longrightarrow C_6H_4\left\langle\begin{matrix}N\\NH\end{matrix}\right\rangle CCH_3$$

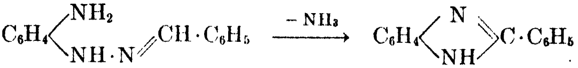
Monoalkyl-*o*-diamines give benzimidazoles (*Fischer*, Ber. **25,** 2826). For the reaction of formaldehyde with *o*-phenylenediamine, see *Fischer*, Ber. **32,** 245.

By a similar course of reaction N-arylaminobenzimidazoles (III) are formed from *o*-aminoazo compounds (I) and aldehydes; the Schiff bases (II) first formed isomerize in boiling glacial acid to benzimidazoles (*Fischer*, J.pr. **104,** 102; **107,** 16):



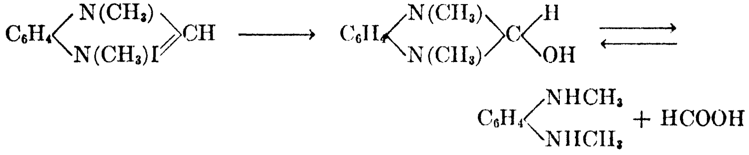
(I) (II) (III)

(*4*) 2-Phenylbenzimidazole is prepared by warming *s*-benzylidene-*o*-aminophenylhydrazine with dilute mineral acids (*Franzen*, Ber. **40,** 909):



$$C_6H_4\left<\begin{matrix}NH_2\\ NH\cdot N\end{matrix}\right.\!\!=CH\cdot C_6H_5 \xrightarrow{-NH_3} C_6H_4\left<\begin{matrix}N\\ NH\end{matrix}\right>C\cdot C_6H_5$$

Properties.—The benzimidazoles closely resemble the imidazoles in behavior (p. 126), although the acidity of the imino group, outweighs the basicity, the benzimidazoles being soluble in aqueous alkali. Alkyl radicals are readily introduced into the imino group, acyl radicals somewhat less readily. The N-alkylbenzimidazoles add alkyl iodides, and the addition products are rearranged by alkali to 1,3-dialkyl-2-hydroxybenzimidazolines; the latter are converted by boiling aqueous sodium hydroxide to dialkyl-*o*-phenylenediamines and formic acid, from which components they can be regenerated by warming:

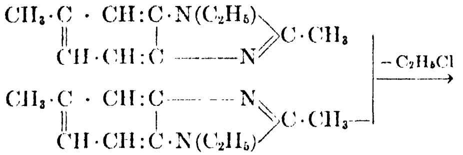


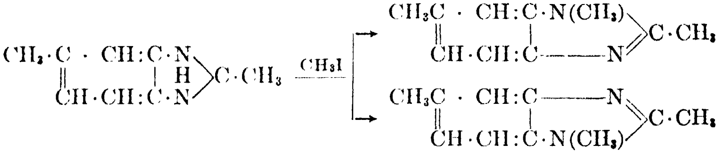
$$C_6H_4\left<\begin{matrix}N(CH_2)\\ N(CH_3)I\end{matrix}\right>CH \longrightarrow C_6H_4\left<\begin{matrix}N(CH_3)\\ N(CH_3)\end{matrix}\right>C\left<\begin{matrix}H\\ OH\end{matrix}\right. \rightleftarrows C_6H_4\left<\begin{matrix}NHCH_3\\ NHCH_3\end{matrix}\right. + HCOOH$$

This fission is facilitated by nitro groups in the benzene ring, and hindered by alkyl substituents in the benzene or imidazole rings (*Fischer*, J.pr. **73**, 419). Just as in the case of the imidazoles, benzoyl chloride and sodium hydroxide, even at 0°, attack the imidazole ring of the simpler benzimidazoles, producing dibenzoyl-*o*-diamines (*cf. Heller*, Ber. **37**, 3116). The benzimidazoles are fairly resistant to reducing and oxidizing agents. Some amino derivatives give substantive azo dyes [*Lellmann, Hailer*, Ber. **26**, 2760; *Pinnow, Wiskott*, Ber. **32**, 898; *Kym*, Ber. **37**, 1070; *Muttelet*, Ann.chim.phys. [7] **14** (1898), 391, 433], in which they resemble the corresponding benzoxazoles (p. 138) and benzothiazoles (p. 143).

BENZIMIDAZOLE, *o-phenyleneformamidine*, $C_6H_4\left<\begin{matrix}N\\ NH\end{matrix}\right>CH$, m.p. 167°, is prepared from formic acid and *o*-phenylenediamine and by the action of chloroform and potassium hydroxide on *o*-phenylenediamine (*Grassi-Cristaldi, Lombardi*, Gazz. **25**, 1, 224); it is partially oxidized by potassium permanganate to imidazoledicarboxylic acid. **1-Methylbenzimidazole**, m.p. 61°, is best prepared from N-methyl-*o*-phenylenediamine; methyl iodide, $C_6H_4[N_2(CH_3)_2I]CH$, m.p. 144°. **1-Vinylbenzimidazole**, oil, b.p. 146° (12 mm.) (*Meisen, Wieger*, J.pr. **102**, 45). **2-Methylbenzimidazole**, *o-phenyleneacetamidine*, $C_6H_4(N_2H)C\cdot CH_3$, m.p. 176°. **2-Phenylbenzimidazole**, *phenylenebenzamidine*, $C_6H_4(N_2H)C\cdot C_6H_5$, m.p. 291°, is also formed by rearrangement of *o*-aminobenzophenone oxime [*Auwers, v. Mayenburg*, Ber. **24**, 2386; *Wheeler*, Am.Chem.J. **17** (1897), 397]. **2-(*o*-Aminophenyl)-benzimidazole**, $C_6H_4(N_2H)CC_6H_4[2]NH_2$, m.p. 211°, condenses with formic acid to form an anhydro compound: **benzimidazo[1,2-*c*]quinazoline**, $\begin{matrix}N{=\!=}C\cdot C_6H_4\cdot N\\ |\quad\ \ |\qquad\quad \|\\ C_6H_4\cdot N\text{———}CH\end{matrix}$, m.p. 227°; with nitrous acid the corresponding triazo compound, m.p. 208°, is formed (*v. Niementowski*, Ber. **32**, 1456). For **2-(*o*-, *m*- and *p*-aminophenyl)-benzimidazole** and their reactions, see *Miklaszewski, v. Niementowski*, Ber. **34**, 2953.

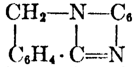
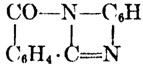
2,5(or 2,6)-Dimethybenzimidazole, $CH_3C_6H_3(N_2H)CCH_3$, m.p. 199°, from 1,3,4-toluenediamine with glacial CH_3CO_2H or CH_3CHO. Application of method *2* (see p. 132) to the two nitroethyltoluidines, $CH_3[1]C_6H_3[3]NO_2[4]NHC_2H_5$ and $CH_3[1]C_6H_3[4]NO_2[3]NHC_2H_5$, gives two isomeric **1-ethyl-2,*Bz*-dimethylbenzimidazoles**, m.p. 87° and 93°; when the hydrochlorides of these isomers are heated, ethyl chloride is eliminated, and the same 2,5(or 2,6)-dimethylbenzimidazole is obtained from each of the two. 2,5(or 2,6)-Dimethylbenzimidazole and methyl iodide give two isomeric **1,2,*Bz*-trimethylbenzimidazoles**, m.p. 123° and 142°, which are also obtained from the two N-methyl-*o*-toluenediamines with glacial acetic acid; with methyl iodide they both form the same addition product, m.p. 221° (*Fischer*, J.pr. **73**, 424). The following equations illustrate these relationships:





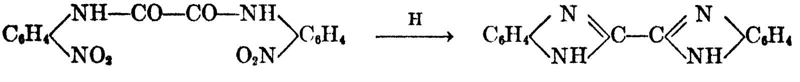
Like the 4(5)-alkylimidazoles (p. 127), 2,5(or 2,6)-dimethylbenzimidazole is virtually a tautomeric substance (*cf. Fischer, Rigaud*, Ber. **34**, 4202). With silver nitrate it gives a silver salt, $C_7H_6(C_2H_3N_2Ag)$. Chloride of lime attacks the imine hydrogen, replacing it with a chlorine atom, which, in boiling benzene solution, changes place with a hydrogen atom on the benzene ring; this process of chlorination can be repeated until all the hydrogen atoms of the benzene nucleus are replaced by chlorine, and **1-chloro-2,***Bz***-dimethyltrichlorobenzimidazole,** $CH_3 \cdot C_6Cl_3(N_2Cl)C \cdot CH_3$, is obtained. *1-Acetyl-2,Bz-dimethylbenzimidazole*, $C_7H_6(C_2H_3N_2 \cdot COCH_3)$, is formed from the silver salt with acetyl chloride, and the *1-benzoyl compound*, m.p. 92°, from the base with benzoyl chloride. Benzoyl chloride and aqueous sodium hydroxide decompose it to dibenzoyltoluenediamine. With benzaldehyde it condenses to 2-styryl-5(6)-methylbenzimidazole, $C_7H_6(N_2H)C \cdot CH{:}CHC_6H_5$, and with phthalic anhydride to a *phthalone* (*cf.* quinophthalone), which is oxidized by $KMnO_4$ to *5(6)-methylbenzimidazole-2-carboxylic acid*, $C_8H_7N_2 \cdot COOH$.

Naphth[1,2]imidazole, $C_{10}H_6(N_2H)CH$, m.p. 174°, is converted by means of chromic acid to **4,5-benzimidazoledicarboxylic acid,** $(COOH)_2[4,5]C_6H_2(N_2H)CH$ (numbering, p. 131), m.p. 251° (*Fischer*, Ber. **32**, 1312). **1-Methylphenanthr[9,10]imidazole,** *epiosin*, $(C_6H_4)_2C_2(N_2 \cdot CH_3)CH$, m.p. 195°, is prepared from 9-hydroxy-10-phenanthrylamine (Vol. III) by heating with alcoholic methylamine solution; it has a physiological action similar to morphine [*Vahlen*, Arch.exp. Path.Pharm. **47** (1902), 368]. For polymeric benzimidazoles, see *Fischer, Wreszinski*, Ber. **25**, 2712.

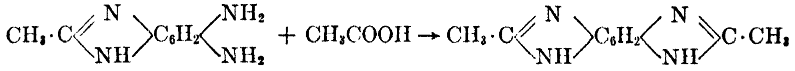
11-Isoindolo[2,1-*a*]benzimidazole, *benzylenebenzimidazole*,  $\begin{array}{l} CH_2{-}N{-}C_6H_4 \\ C_6H_4 \cdot C{=}N \end{array}$, m.p. 210°, is formed by the condensation of phthalaldehyde with *o*-phenylenediamine. By careful oxidation with $KMnO_4$ it can be converted to **11-isoindolo[2,1-*a*]benzimidazol-11-one,**  $\begin{array}{l} CO{-}N{-}C_6H_4 \\ C_6H_4 \cdot C{=}N \end{array}$, yellow needles, m.p. 213°, which is the lactam of 2-phenylimidazole-4-carboxylic acid, m.p. 266°; the latter is also obtained by condensation of *o*-phenylenediamine with phthalic anhydride or *o*-phthalaldehydic acid and by reduction of N-phenyl-*o*-nitrophthalimide (*Rupe, Thiess*, Ber. **42**, 4287).

Benzimidazole-2-propionic acid, m.p. 236° (with foaming), from *o*-phenylenediamine and succinic acid (*Willstätter, Stoll*, Ann. **415**, 37); ethyl ester, m.p. 136°; methyl ester, m.p. 145°.

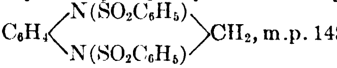
2,2′-Bibenzimidazole is formed by reduction of *o,o′*-dinitroöxanilide (*Buchta*, Ann. **209**, 257):



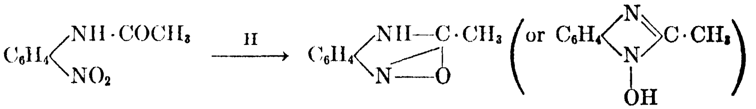
Benzobisimidazoles are prepared from *o*-diaminobenzimidazoles with carboxylic acids (*Nietzki, Schmidt*, Ber. **22**, 1652):



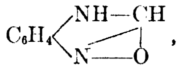
$$CH_3\cdot C\left\langle{N \atop NH}\right\rangle C_6H_2\left\langle{NH_2 \atop NH_2}\right. + CH_3COOH \rightarrow CH_3\cdot C\left\langle{N \atop NH}\right\rangle C_6H_2\left\langle{N \atop NH}\right\rangle C\cdot CH_3$$

HYDROGENATED BENZIMIDAZOLES, BENZIMIDAZOLINES, have not been identified with certainty. The primary products resulting from the interaction of monoalkylated *o*-diamines and aldehydes are probably benzimidazolines; they are readily converted to benzimidazoles by elimination of hydrogen (*Fischer*, Ber. **25**, 2827). The condensation products of acetoacetic ester with *o*-toluenediamine behave similarly (*Autenrieth, Hinsberg*, Ber. **25**, 606). The action of methylene iodide on N,N′-diphenylsulfonyl-*o*-phenylenediamine yields **1,3-diphenylsulfonylbenzimidazoline,**  $C_6H_4\left\langle{N(SO_2C_6H_5) \atop N(SO_2C_6H_5)}\right\rangle CH_2$, m.p. 148° (*Hinsberg, Strupler*, Ann. **287**, 220).

The compounds obtained by reduction of acylated *o*-nitranilines with ammonium sulfide or tin and hydrochloric acid are apparently derivatives of hydrobenzimidazoles; when heated with zinc dust they yield benzimidazoles (*v. Niementowski*, Ber. **43**, 3012):

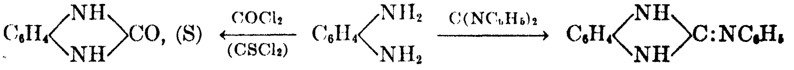


$$C_6H_4\left\langle{NH\cdot COCH_3 \atop NO_2}\right. \xrightarrow{H} C_6H_4\left\langle{NH—C\cdot CH_3 \atop N——O}\right. \left(\text{or } C_6H_4\left\langle{N \atop \underset{OH}{N}}\right\rangle C\cdot CH_3\right)$$

Oxazirobenzimidazole,  $C_6H_4\left\langle{NH—CH \atop N——O}\right.$, m.p. 210°, from *o*-nitroformanilide with $(NH_4)_2S$, is easily rearranged by various reagents to the isomeric 2(3)-benzimidazolone (see below). **2-Methyloxazirobenzimidazole,** m.p. 251°.

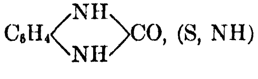
BENZIMIDAZOLINOLS are formed from the alkyl halide addition products of N-alkylbenzimidazoles with aqueous alkali, and from N,N′-dialkyl-*o*-phenylenediamines with carboxylic acids. Their reversion to the latter components is discussed above. With hydriodic acid they regenerate the alkyl iodides of the 1-alkylbenzimidazoles. Oxidation converts them very readily to the stable 2(3)-benzimidazolones (see below). **1,3-Dimethylbenzimidazolinol,** $C_6H_4(NCH_3)_2CH(OH)$, m.p. 74°, when boiled with aq. sodium hydroxide is split into formic acid and N,N′-dimethyl-*o*-phenylenediamine. With acetic anhydride the latter gives **1,2,3-trimethylbenzimidazolinol,** $C_6H_4(NCH_3)_2C(OH)CH_3$, m.p. 164°. **5-Nitro-1,3-dimethylbenzimidazolinol,** m.p. 128°, from the methyl iodide with soda or ammonia, is decomposed even by cold aqueous sodium hydroxide. **1-Phenyl-3-methylbenzimidazolinol,** m.p. 168°, resistant to splitting. **1,3,4,6-Tetramethylbenzimidazolinol,** $(CH_3)_2C_6H_2(NCH_3)_2CH(OH)$, m.p. 135°, decomposes when heated with alcoholic sodium hydroxide solution under pressure (*Fischer*, Ber. **34**, 936; J.pr. **73**, 419; *Fischer, Rigaud*, Ber. **34**, 4202; *Fischer, Hess*, Ber. **36**, 3967).

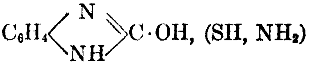
OXO-, THIO- and **IMINOBENZIMIDAZOLINES** are cyclic phenyleneureas, thioureas, and guanidines; they are prepared from *o*-diamines with $COCl_2$ and $CSCl_2$ or CS_2, with urea and thiourea or ammonium thiocyanate, or with phenyl isothiocyanate and carbodiphenylimide (see below):



$$C_6H_4\left\langle{NH \atop NH}\right\rangle CO,\ (S) \xleftarrow[(CSCl_2)]{COCl_2} C_6H_4\left\langle{NH_2 \atop NH_2}\right. \xrightarrow{C(NC_6H_5)_2} C_6H_4\left\langle{NH \atop NH}\right\rangle C{:}NC_6H_5$$

In many respects these compounds behave as hydroxy, mercapto and amino derivatives of benzimidazoles, and therefore may have either of these two formulas:

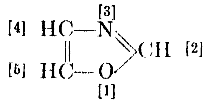
(I)  $C_6H_4\left\langle{NH \atop NH}\right\rangle CO$, (S, NH)

 $C_6H_4\left\langle{N \atop NH}\right\rangle C\cdot OH$, (SH, NH_2) (II)

2(3)-Benzimidazolone, *o-phenyleneurea*, $C_6H_4(N_2H_2)CO$, m.p. 308°, can also be prepared from *o*-aminophenylurethan (*Liebermann*, Ber. **12**, 1296; *Hartmann*, Ber. **23**, 1047; *Kym*, J.pr. **75**, 323). **Methyl-2(3)-benzimidazolone**, $C_7H_6(N_2H_2)CO$, m.p. 290°, also from **2-ethoxymethylbenzimidazole**, $C_7H_6(N_2H){:}C(OC_2H_5)$, m.p. 163°, the product of the reaction of imidocarbonic acid ester and *o*-toluenediamine, by saponification. **1,3-Dimethyl-2(3)-benzimidazolone**, $C_6H_4(NCH_3)_2CO$, m.p. 110°, is formed by oxidation of 1,3-dimethylbenzimidazolinol (see above and *Pinnow*, *Sämann*, Ber. **32**, 2187).

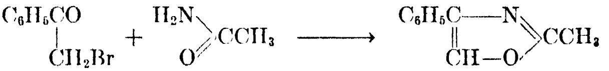
Thiobenzimidazolone, *o-phenylenethiourea*, $C_6H_4(N_2H_2)CS$, m.p. 298° (dec.), from phenylenediamine thiocyanate (*Lellmann*, Ann. **221**, 9; **228**, 244). **Benzimidazolone 2-anil**, *o-phenylenephenylguanidine*, $C_6H_4(CN_3H_2C_6H_5)$, m.p. 188°, from carbodiphenylimide and *o*-phenylenediamine (*Gabriel*, *Heymann*, Ber. **23**, 2498).

9. OXAZOLES



In the older literature, μ is used for position 2, and α and β for positions 4 and 5. See page 143.

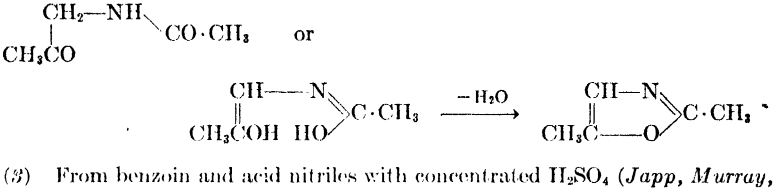
The oxazoles are isomers of the isoxazoles. They are prepared: (*1*) By condensation of α-halogeno ketones with carboxylic acid amides (*Lewy*, Ber. **20**, 2576; **21**, 2195):



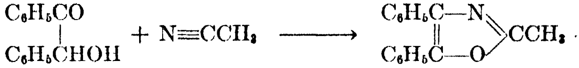
2-Methyl-4-phenyloxazole

The ketone and the amide probably react in the hydroxyl form (*cf.* p. 90, general syntheses of the azoles).

(*2*) From acylated α-amino ketones by the action of PCl_5 or concentrated H_2SO_4 (*Gabriel*, Ber. **43**, 1283; *Kohn*, *Berm*, J. **95**, 2167), analogous to the formation of furans from 1,3-dicarbonyl compounds (p. 15):

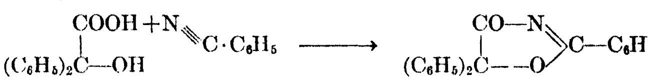


(*3*) From benzoin and acid nitriles with concentrated H_2SO_4 (*Japp*, *Murray*, J. **63** (1893), 469):



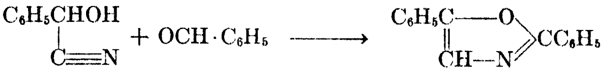
2-Methyl-4,5-diphenyloxazole

Triphenyloxazolone, m.p. 136°, is formed from benzilic acid and benzonitrile with concentrated sulfuric acid (*Japp*, *Findlay*, Proc.Chem.Soc. **15** (1899), 165):



2,5,5-Triphenyl-4-oxazolone

(*4*) From mandelonitrile and its homologues with benzaldehyde in the presence of gaseous hydrogen chloride (*Minovici*, Ber. **29**, 2097):



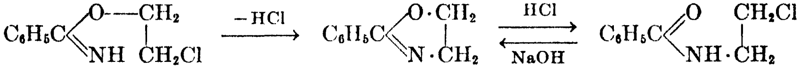
2,5-Diphenyloxazole

Properties.—The oxazoles are weak bases. The lower members of the series smell like pyridine and are miscible with water. When evaporated with hydrochloric acid they decompose into carboxylic acids and amines. Oxidizing and reducing agents open the oxazole ring of some derivatives easily, while others are more stable. The parent substance of the group is not known.

4-Phenyloxazole, m.p. 46°, b.p. 222°, is prepared from formamide with ω-bromoacetophenone. **2-Methyl-4-phenyl-** and **4,5-diphenyloxazole,** m.p. 45°, b.p. 242°, and m.p. 44°, b.p. 192–195° (15 mm.), respectively. **5-Methyl-2-phenyloxazole,** b.p. 240°, from benzamide and chloroacetone, is converted by alcoholic NH_3 to phenylmethylimidazole. **2,4-Dimethyloxazole,** b.p. 108°, from acetamide and chloroacetone according to method *1* (see above) (*Oesterreich*, Ber. **30**, 2254). **2,5-Dimethyloxazole,** b.p. 118° (*Gabriel*, Ber. **43**, 1287), from acetaminoacetone and PCl_5. **2-Methyl-5-phenyloxazole,** m.p. 59°, b.p. 255°, from acetaminoacetophenone by method *2*.

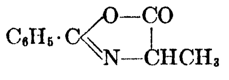
2,5-Diphenyloxazole, m.p. 74°, b.p. over 360°, from benzamide and phenylbromoacetaldehyde by method *3*, from benzoylaminoacetophenone by method *2*, and from mandelonitrile and benzaldehyde by method *4*, together with benzalmalonamide (*Fischer*, Ber. **29**, 205). Oxidation with chromic acid converts it to N-*phenylglyoxylylbenzamide*, $C_6H_5CO\cdot CO\cdot NH\cdot COC_6H_5$, and reduction with sodium and alcohol, to 1-*phenyl-2-benzylaminoethanol*, $C_6H_5CH_2\cdot NH\cdot CH_2\cdot CH(OH)C_6H_5$. When heated with ammonia it gives diphenylimidazole. **2,4,5-Triphenyloxazole,** *benzilam*, m.p. 115°, has been observed among the products of the reaction of ammonia and benzil (*Pinner*, Ber. **35**, 4137); it is more advantageously prepared from benzoyldesylamine, $C_6H_5\cdot CO\cdot CH(C_6H_5)\cdot NH\cdot CO\cdot C_6H_5$, by brief heating with concentrated H_2SO_4, according to method *2* (p. 136).

DIHYDROÖXAZOLES, OXAZOLINES, are formed by condensation of the β-halogenoalkylamides of carboxylic acids by means of alkali (*Gabriel*, Ber. **22**, 2220). Benzimidyl chloroethyl ether when warmed gently rearranges to the hydrochloride of phenyloxazoline; at 100° the latter rearranges to chloroethylbenzamide (*Wislicenus, Körber*, Ber. **35**, 164):



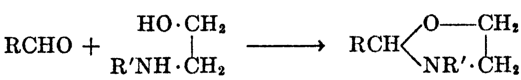
2-Phenyloxazoline, b.p. 243°, is split by sodium and amyl alcohol to 2-(benzylamino)-ethanol, $HOCH_2\cdot CH_2\cdot NH\cdot CH_2\cdot C_6H_5$ (*Gabriel, Stelzner*, Ber. **29**, 2382). **2-Methyloxazoline,** b.p. 110°, *picrate* m.p. 159° (*Gabriel, Heymann*, Ber. **23**, 2502). **2,4-Dimethyloxazoline,** b.p. 118°, from β-bromopropylacetamide. **4-Methyl-2-phenyloxazoline,** b.p. 244°, is also obtained from allylbenzamide, $C_6H_5CO\cdot NH\cdot CH_2\cdot CH{:}CH_2$, with H_2SO_4 (*Eitner, Wetz*, Ber. **26**, 2840; *Uedinck*, Ber. **32**, 967).

The lactone-like anhydrides of α-benzoylamino fatty acids such as

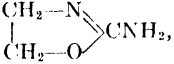


are oxodihydroöxazoles or oxazolones. **2,5,5-Triphenyl-4-oxazolone,** m.p. 136°; for its synthesis according to method *3*, see above.

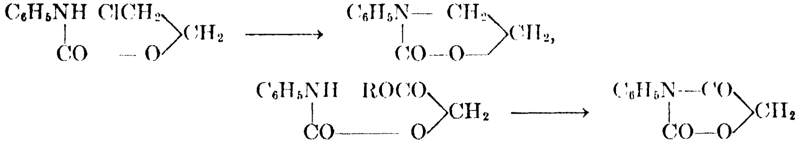
TETRAHYDROÖXAZOLES, OXAZOLIDINES. These are the condensation products of aldehydes with amino alcohols (*Knorr, Matthes*, Ber. **34**, 3484):



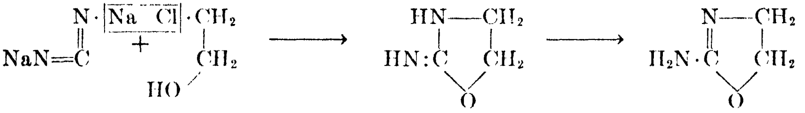
They are distillable liquids, which are readily hydrolyzed into their components. **3-Methyloxazolidine,** b.p. 100°; **2-methyloxazolidine,** b.p. 141°; **2,3-dimethyloxazolidine,** b.p. 109°; **2-phenyloxazolidine,** b.p. 284°. Another member of this group is the product of the reaction of 1-aminopropylene glycol and benzaldehyde, **2-phenyl-5-(hydroxymethyl)-oxazolidine**, m.p. 75–79°, which is of use in the preparation of glycerides (*Bergmann, Brand, Dreyer*, Ber. **54**, 936, 949; *Bergmann*, Z.physiol.Chem. **137**, 27; Vol. I, p. 585).

AMINOÖXAZOLINES or **iminoöxazolidines** (see below) are also known as alkylene-β-ureas: **2-aminoöxazoline**, , picrate m.p. 158°, and **2-amino-5-methyloxazoline**, picrate m.p. 186°, obtained from β-bromoethyl- and β-bromopropylamine with potassium cyanate. **4,5-Diphenyl-2-aminoöxazoline**, m.p. 154°, from diphenylhydroxyethylamine with potassium cyanate (*Söderbaum*, Ber. **28**, 1899).

OXOTETRAHYDROÖXAZOLE derivatives result from the elimination of HCl from β-halogenoalkyl esters of carbamic acid [*Johnson, Guest*, Am.Chem.J. **44** (1911), 453], and dioxo derivatives from the phenylurethans of α-hydroxycarboxylic acid esters (*Lambling*, C.r. **127**, 188; Bull. [3] **27**, 606):



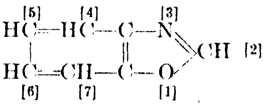
The action of 1,2-chlorohydrins, their homologues or alkylene oxides on sodium cyanamide produces **2-iminoöxazolidines** (*Fromm, Honold*, Ber. **55**, 902; *Josephson*, Ann. **467**, 292):



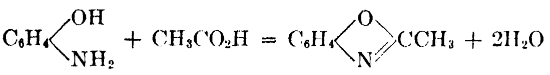
(I) (II)

The iminoöxazolidines (I) are tautomeric substances which can also react as 2-aminoöxazolines (II) (see above); with phenyl isothiocyanate they give two isomeric series of phenylthioureas (*v. Auwers, Hilliger, Wulf*, Ann. **429**, 241).

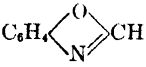
10. BENZOXAZOLES



As benzimidazoles are formed from *o*-phenylenediamines, so benzoxazoles are prepared from *o*-aminophenols, by heating with carboxylic acids or their derivatives:

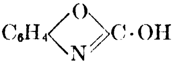


The benzoxazoles, also known as alkenylaminophenols, are weak bases; when warmed with acids they are split into their components. Several benzoxazole derivatives are substantive cotton dyes (*Lellmann, Ebel*, Ber. **28**, 1127; *Kym*, Ber. **32**, 1427).

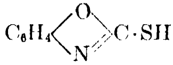
BENZOXAZOLE, *methenylaminophenol*, , m.p. 31°, b.p. 183°,

volatile with steam, is obtained by heating *o*-aminophenol with formic acid or by heating *o*-formylaminophenol to 160–170°. It hydrolyzes to formylaminophenol in boiling water. **Benzoxazole** is similar to the isomeric anthranil (*Bamberger*, Ber. **36,** 2054). When heated with CH_3I it forms a methyl iodide, m.p. 183° (dec.), which is split by dilute mineral acid to N-methyl-*o*-aminophenol. Benzoxazoles are also formed from many oximes of aromatic *o*-hydroxyketones by *Beckmann* rearrangement, if the oxime is in the *anti* form in relation to the hydroxyl substituted aromatic nucleus (*v. Auwers, Jordan*, Ber. **58,** 26; *Meisenheimer, Zimmermann, v. Kummer*, Ann. **446,** 205; *Meisenheimer, Hanssen, Wächterowitz*, J.pr. **119,** 315). **2-Methylbenzoxazole,** *ethenylaminophenol*, b.p. 201°. **2-Phenylbenzoxazole,** m.p. 103°, is also prepared by reduction of benzoyl-*o*-nitrophenol [*Ladenburg*, Ber. **9,** 1526; *Wheeler*, Am.Chem.J. **17** (1896), 397; *Hübner*, Ann. **210.** 384]. **2,4,6-Trimethylbenzoxazole,** m.p. 28.5°, from the *anti*-oxime of 2-acetyl-3,5-xylenol by the Beckmann rearrangement (*v. Auwers, Jordan*, Ber. **58,** 32); **5-methyl-2-phenylbenzoxazole,** m.p. 104°. **2-Phenyl-5,7-dimethylbenzoxazole,** m.p. 99–100° (*Meisenheimer, Hanssen, Wächterowitz*, J.pr. **119,** 340). **6-Methyl-2-(*p*-aminophenyl)-benzoxazole,** m.p. 188°, is prepared by reduction of *p*-nitrobenzoyl-*m*-nitro-*p*-cresol; its diazo compound couples with 2-naphthol and similar compounds to give carmine-red, acid-stable, substantive cotton dyes. For the preparation and properties of a number of 2-alkylbenzoxazoles, see *Skraup*, Ann. **419,** 1.

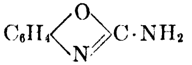
Hydroxy and mercapto derivatives of benzoxazoles are prepared from *o*-aminophenols with $COCl_2$ or ClCOOR and CS_2 or $CSCl_2$, amino derivatives from the hydroxy or mercapto derivatives by heating with amines. As in the case of the analogous benzimidazole compounds (p. 135), two formulas are possible for these compounds:



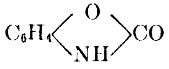
2-Benzoxazolol



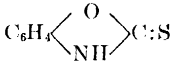
2-Benzoxazolethiol



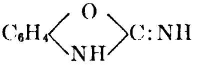
2-Aminobenzoxazole



2(3)-Benzoxazolone



2-Thio-2(3)-benzoxazolone



2-Imino-2,3-benzoxazoline

Alkyl derivatives of both forms of hydroxybenzoxazole have been prepared; the members of one series are O-alkyl derivatives, or *lactim* ethers, while the members of the other series are N-alkyl derivatives, or *lactam* ethers. The aminobenzoxazoles also form isomeric alkyl derivatives.

2-Benzoxazolol, *carbonylaminophenol*, m.p. 137°, is also prepared by the action of thionyl chloride on salicylhydroxamic acid (*Beckmann* rearrangement) (*Marquis*, C.r. **143,** 1163) and by heating acetylsalicylhydroxamic acid or *o*-acetoxybenzoic acid azide in benzene solution (*Lindemann, Schultheis*, Ann. **451,** 243). It is insoluble in alkali. With ethyl iodide it gives an N-ethyl derivative, **1-ethyl-2-benzoxazolone,** m.p. 29°; **2-ethoxybenzoxazole,** b.p. 225–230°, is obtained from imidocarbonic acid ether with *o*-aminophenol (*Sandmeyer*, Ber. **19,** 2655). **1-Benzoyl-2-benzoxazolone,** m.p. 174° (*Ransom*, Ber. **31,** 1055). A **dibromobenzoxazolone,** $C_6H_2Br_2(CO_2NH)$, m.p. 255°, is formed from salicylamide with KOBr (*van Dam*, Rec. **18,** 408). **2-Benzoxazolethiol** (formula given above), m.p. 193–196°, soluble in alkalies and ammonia, is prepared from aminophenol hydrochloride with potassium xanthogenate or from *o*-aminophenol and CS_2 in alcoholic solution.

2-Aminobenzoxazole, m.p. 130°, isomeric with 2(3)-benzimidazolone (p. 136), is prepared from *o*-hydroxyphenylthiourea by elimination of H_2S by means of HgO, and from benzoxazole by treatment with hydroxylamine (*Skraup*, Ann. **419,** 1).

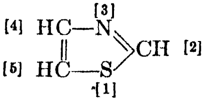
Benzoxazolyl alkyl ketones are not known, but 2-benzoylbenzoxazole is obtained from 2-benzylbenzoxazole through the oximino derivative (*Skraup, Moser*, Ber. **55,** 1096).

2-Benzoxazolecarboxylic acid, m.p. 85°, is prepared by oxidation of 2-methylbenzoxazole, or more smoothly from 2-*o*-hydroxyphenylbenzoxazole with potassium permanganate (*Skraup, Moser*, Ber. **55,** 1091). The silver and mercurous salt are sparingly soluble in water.

Naphthoxazoles: *Fischer*, J.pr. **73**, 438; *v. Meyer*, J.pr. **92**, 258; *Jacobson*, Ber. **21**, 414; *Jacobson*, *Schenke*, Ber. **22**, 3241.

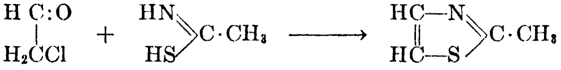
Dioxoanthroxazoles: *Ullmann*, *Junghaus*, Ann. **399**, 331.

11. THIAZOLES



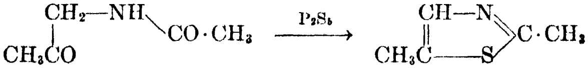
In the older literature μ indicates the 2-position, and α and β indicate the 4- and 5-positions. See page 143.

As the oxazoles are obtained from the carboxylic acid amides, so the thiazoles are formed from the thioamides with α-halogeno aldehydes or ketones (*cf.* p. 136):



Chloroacetaldehyde Thioacetamide 2-Methylthiazole

The preparation of thiazoles from acylated α-amino ketones by heating with phosphorus sulfide is analogous to the formation of thiophenes from 1,3-dioxo compounds (p. 15) (*Gabriel*, Ber. **43**, 1283):



In the same way 5-alkoxythiazoles are obtained from acylated α-amino carboxylic acid esters and P_2S_5 (*Miyamichi*, J.Pharm.Soc.Japan **1926**, No. 528, 16).

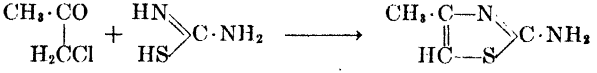
Thiazole and its homologues are prepared also from 2-aminothiazoles (p. 141) through the diazo compounds, as benzene is obtained from aniline.

Behavior.—While thiophene resembles benzene, thiazole and its derivatives correspond in their physical and some of their chemical properties to the pyridines. Thiazole may be considered to be derived from pyridine by replacement of a CH=CH-group by an S-atom (p. 4). The thiazoles are tertiary bases and form addition products with alkyl iodides. They are usually resistant to oxidizing agents; $KMnO_4$, however, splits out the sulfur as H_2SO_4. For spectrochemical data on the thiazoles, see *v. Auwers*, *Ernst*, Z.physik.Chem. **122** (1926), 217.

THIAZOLE, b.p. 117°, with an odor like pyridine, is prepared from 2-aminothiazole with N_2O_3 and alcohol, and from chloroacetaldehyde and thioformamide (*Willstätter*, *Wirth*, Ber. **42**, 1918); $C_3H_3NS \cdot HCl \cdot AuCl_3$, m.p. 248-250° (dec.); $C_3H_3NS \cdot HgCl_2$, m.p. 202-204°. **5-Methylthiazole**, m.p. 232°, from the amino compound and also from methylthiazolol by distillation with zinc dust (*Popp*, Ann. **250**, 279); the isomeric 2-**methylthiazole**, b.p. 128°, with an odor like picoline, is formed from monochloroacetaldehyde and thioacetamide. **2,4-Dimethylthiazole**, b.p. 145°, from chloroacetone and thioacetamide, is decomposed by reduction with sodium and alcohol to ethylisopropylamine and H_2S. **2,5-Dimethylthiazole**, b.p. 153° (758 mm.), from acetamidoacetone and P_2S_5. The methyl group in the 2-position possesses a reactivity similar to a methyl group on a pyridine ring (*Schuftan*, Ber. **27**, 1009). **2,4,5-Trimethylthiazole**, b.p. 167°; 4-**phenylthiazole**, m.p. 52°, b.p. 273°. **2-Methyl-5-phenylthiazole**, m.p. 81°, from acetamidoacetophenone and P_2S_5; **2-phenyl-5-methylthiazole**, b.p. 283°, from benzoylaminoacetone and P_2S_5; **2,5-diphenylthiazole**, m.p. 104°, from benzoylaminoacetophenone and P_2S_5. **2,4-Diphenylthiazole**, b.p. 153° (758 mm.). **2,4,5-Triphenylthiazole**, m.p. 87°, from thiobenzamide and bromodesoxybenzoin or desyl bromide.

Halogenothiazoles are obtained from diazothiazoles (page 141) with concentrated hydrohalogen acids: **2-chlorothiazole**, b.p. 145°; **2-bromothiazole**, **b.p.** 171°.

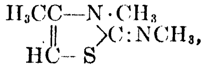
2-Aminothiazoles are formed from α-halogeno ketones with thioureas (*pseudo form*):



2-Amino-4-methylthiazole

s-Dialkylthioureas give compounds which are derived from iminothiazoline; for the isomeric monoalkylaminothiazoles, see *Näf*, Ann. **265**, 110. The aminothiazoles are similar to the primary aromatic amines; they can be converted to diazo compounds, and through these, to halogenothiazoles, thiazoles, and thiazolecarboxylic acids.

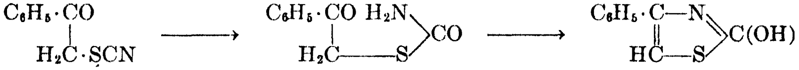
2-Aminothiazole, m.p. 90°, prepared from α,β-dichlorodiethyl ether (enters the reaction as monochloroacetaldehyde) and thiourea. Its nitrate reacts with N_2O_3 to give thiazolediazonium hydroxide, $C_3H_2(N{:}NOH)NS$, which couples with resorcinol, naphthol, and the like, to form yellow to brown azo dyes (*Jaeckle*, Ann. **246**, 40). **2-Amino-4-methylthiazole**, m.p. 42°, b.p. 136° (30-40 mm.), from chloroacetone with thiourea or ammonium thiocyanate (*Hantzsch, Weber*, Ber. **20**, 3127); **2-amino-4-phenylthiazole**, similarly from α-chloroacetophenone (*Schatzmann*, Ann. **261**, 14). **3,4-Dimethyl-2-methyliminothiazoline,**



m.p. 96°, from chloroacetone and *s*-dimethylthiourea.

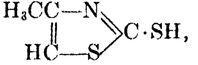
The similarity between the 2-aminothiazoles and primary aromatic amines, which is indicated in the diazotization of the amino group, is also apparent in the reaction with aromatic aldehydes, which produces derivatives of dithiazolylphenylmethane; the latter can be converted to dyes analogous to the triphenylmethane dyes [*Bogert, Chertcoff*, Proc.Nat.Acad.Sci.U.S. **10** (1924), 418].

Thiazolols result from the isomerization of α-thiocyano ketones when allowed to stand in aqueous bicarbonate solution (*Tcherniac*, Ber. **25**, 2608) or when warmed with mineral acid (*Hantzsch*, Ber. **60**, 2537):

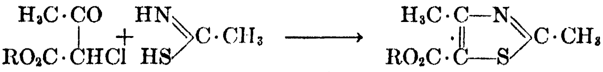


Thiocyanoacetophenone — Carbamylthioacetophenone — 4-Phenyl-2-thiazolol, m.p. 204°

4-Methyl-2-thiazolol, m.p. 106°, is prepared from its carboxylic acid (see below) by decarboxylation, and from thiocyanoacetone with alkalis (*Arapedes*, Ann. **249**, 16; *Wohmann*, Ann. **259**, 297; *Tcherniac*, Ber. **25**, 3648).

Mercaptothiazoles are formed by heating α-chloro ketones with ammonium dithiocarbamate. **4-Methyl-2-thiazolethiol,**  m.p. 90°; **4-phenyl-2-thiazolethiol**, m.p. 168° (*Pinnow*, Ber. **26**, 604).

Thiazolecarboxylic acids. Their esters are produced by condensation of chloroacetoacetic ester, chloroöxalylacetic ester, and the like with thioamides:



2,4-Dimethylthiazole-5-carboxylic acid ester

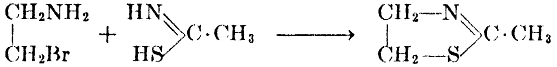
Amino-, hydroxy- and **mercaptothiazolecarboxylic acids** are formed by similar reactions as amino-, hydroxy- and mercaptothiazoles, the corresponding oxocarboxylic acid derivatives being used in place of the α-halogeno or α-thiocyano ketones.

4-Methyl-5-thiazolecarboxylic acid, m.p. 267°; its ester is obtained from aminomethylthiazolecarboxylic acid ester (page 142) by conversion to chlorothiazolecarboxylic acid ester and reduction of the latter. **2-Methyl-4,5-thiazoledicar-**

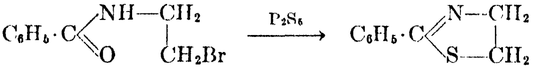
boxylic acid, m.p. 169° (dec.), from chloroöxalylacetic ester and thioacetamide. **2-Methyl-4-thiazoleacetic ester,** $C_3H(CH_3)(CH_2 \cdot COOR)NS$, b.p. 239°, is prepared from γ-bromoacetoacetic ester and thioacetamide.

2-Amino-4-thiazolecarboxylic acid, *sulfuvinic acid,* dec. 245°, from dibromopyruvic acid; its ester, m.p. 173°, from monobromopyruvic acid ester with thiourea (*Steude,* Ann. **261,** 25). **2-Amino-4-methyl-5-thiazolecarboxylic acid ester,** m.p. 175°, from α-chloroacetoacetic ester and thiourea; diazonium hydroxide, m.p. 100° (dec.). **2-Hydroxy-4-methyl-5-thiazolecarboxylic acid ester,** m.p. 128°, is obtained from α-thiocyanoacetoacetic ester (*Wohmann,* Ann. **259,** 284, 298). **2-Mercapto-4-methyl-5-thiazolecarboxylic acid ester,** m.p. 141°, from α-chloroacetoacetic ester and ammonium dithiocarbamate (*Miolati,* Gazz. **23,** I, 575).

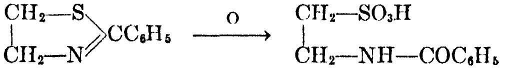
4,5-Dihydrothiazoles or **2-thiazolines** are synthesized: (*1*) From alkylene halides or β-halogenoalkylamines and thioamides (*Gabriel, Heymann,* Ber. **24,** 785; *Gabriel, v. Hirsch,* Ber. **29,** 2610):

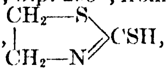


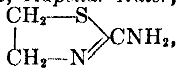
(*2*) From acyl-β-bromoalkylamines with P_2S_5 (*Salomon,* Ber. **26,** 1328):



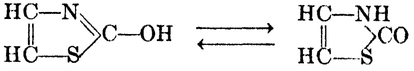
The thiazolines are much more easily split than the thiazoles. **2-Thiazoline,** oil with an odor resembling pyridine, b.p. 139°, is prepared according to method *1* (*Willstätter, Wirth,* Ber. **42,** 1919). **2-Methyl-2-thiazoline,** b.p. 145°, gives β-aminoethanethiol when evaporated with hydrochloric acid. **2-Phenyl-2-thiazoline,** b.p. 276°, is prepared from benzoyl-β-bromoethylamine with P_2S_5 and from aminothiazoline (see below) by treatment with nitrous acid in benzene, analogous to the formation of diphenyl from diazobenzene and benzene (*Gabriel, Leupold,* Ber. **31,** 2833); when oxidized it yields benzoyltaurine (*Gabriel, Heymann,* Ber. **23,** 158):



5-Methyl-2-*o*-tolyl-2-thiazoline, b.p. 295°, from N-β-bromopropyl-*o*-toluylamide and P_2S_5. **2-Thiazoline-2-thiol,**  $\begin{matrix} CH_2\text{—}S \\ | \\ CH_2\text{—}N \end{matrix} \!\!>\! CSH$, m.p. 107°, is formed from bromoethylamine and CS_2 (*Gabriel,* Ber. **22,** 1152) and from ethylenimine (p. 12) and CS_2; when heated with hydrochloric acid it decomposes into CO_2, H_2S, and β-aminoethanethiol (*Gabriel, Leupold,* Ber. **31,** 2836).

Aminothiazolines are alkylene derivatives of pseudothiourea (Vol. I, p. 509) which are usually obtained by rearrangement of allylthioureas (*thiosinamines,* Vol. I, p. 509); they often react as 2-iminothiazolidines (*cf. Fromm, Kapellar-Adler,* Ann. **467,** 243). **2-Amino-2-thiazoline,** *ethylenepseudothiourea,*  $\begin{matrix} CH_2\text{—}S \\ | \\ CH_2\text{—}N \end{matrix} \!\!>\! CNH_2$, m.p. 85°, from bromoethylthiourea (*Gabriel,* Ber. **22,** 1140). **2-Anilino-5-methyl-2-thiazoline,** N-*phenylpropylene-pseudothiourea,* m.p. 117°, from allylphenylthiourea (*Prager,* Ber. **22,** 2991). **2-Piperidyl-5-methyl-2-thiazoline,** b.p. 277°, from N-allyl-N′,N′-pentamethylenethiourea (*Avenarius,* Ber. **24,** 265). **2-Methylamino-4,5-diphenyl-2-thiazoline,** $C_3H_2(C_6H_5)_2NS(NHCH_3)$, m.p. 155°, from diphenylhydroxyethylamine (Vol. III, p. 564) with methyl isothiocyanate (*Söderbaum,* Ber. **28,** 1900).

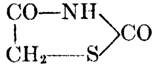
The 2(3)-thiazolones are derivatives of 2,3-dihydrothiazole or 4-thiazoline and are tautomeric with the 2-thiazolols:

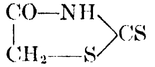


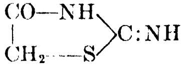
2-Thiazolol 2(3)-Thiazolone

2(3)-Thiazolones are readily formed from thiocyanoketones and concentrated hydrochloric acid (*Hubacher*, Ann. **259**, 250; *Hantzsch*, Ber. **60**, 2537).

The following are derivatives of **tetrahydrothiazole**: 2,4(3,5)-**thiazoledione** (I), m.p. 112°, from thiocyanoacetic acid or thiocyanoacetamide by evaporating with acids (*Miolati*, Gazz. **23**, 1, 90); 2-**thio**-2,4(3,5)-**thiazoledione** *rhodaninic acid* (II), from chloroacetic acid ammonium thiocyanate (see *Zipser*, Mo. **23**, 958; *Andreasch*, Mo. **29**, 399); 2-**imino**-4-**thiazolidone**, *pseudothiohydantoin* (III), m.p. 71° [see Vol. I, p. 510; *cf. Frerichs, Beckurts*, Arch.Pharm. **238** (1900), 317]:

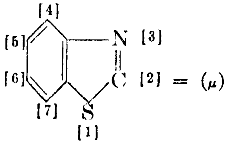
(I) 

(II) 

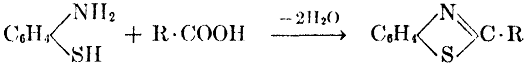
(III) 

2-**Imino**-4-**thiazolidone**-5-**acetic acid**, m.p. 216° (dec.), from chlorosuccinic acid and thiourea, is converted by removal of the NH-group to 2,4(3,5)-**thiazoledione**-5-**acetic acid**, m.p. 169° (*Tambach*, Ann. **280**, 233).

12. BENZOTHIAZOLES



Benzothiazoles, the analogues of benzimidazoles and benzoxazoles, are formed by the following methods. (*1*) From *o*-aminobenzenethiol and carboxylic acids (their chlorides or anhydrides) by elimination of water (*Hofmann*, Ber. **13**, 1224; *Hauser*, Helv. **11**, 198):

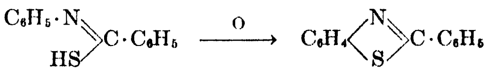


$$C_6H_4\begin{matrix}NH_2\\SH\end{matrix} + R\cdot COOH \xrightarrow{-2H_2O} C_6H_4\begin{matrix}N\\S\end{matrix}C\cdot R$$

The *o*-aminobenzenethiols used as starting materials are readily obtained by the action of sulfur monochloride on the hydrochlorides of aromatic amines (Ger. Pat. 360690, 367344, 1914; Frdl. **XIV**, 908, 912). *o*-Nitrochlorobenzene and its homologues can also be used for the preparation of benzothiazoles by the above method (*Bogert, Snell*, Am. **46**, 1308).

The tendency toward the formation of the benzothiazole ring is so great that under certain conditions hydrogen is spontaneously eliminated. Thus, benzothiazoles are formed from the hydrochlorides of *o*-aminobenzenethiols and aldehydes, in a reaction similar to method *1*, in place of the expected benzothiazolines (*Bogert, Stull*, Am. **47**, 3078).

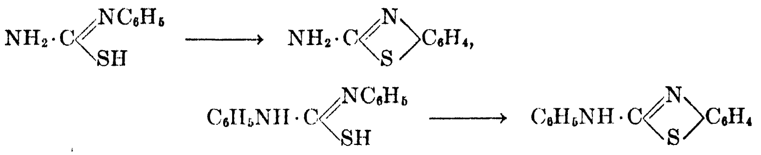
(*2*) From acid anilides by heating with sulfur, or from thioanilides by oxidation with potassium ferricyanide:



Thiobenzanilide 2-Phenylbenzothiazole

Phenylbenzothiazole is also formed when benzylaniline is heated with sulfur; the reaction first gives thiobenzanilide, H_2S being evolved, and this compound reacts according to the above equation (*Wallach*, Ann. **259**, 300).

Similarly, arylthioureas, when treated with bromine in chloroform solution, produce cyclic phenylene-pseudothioureas or 2-aminobenzothiazoles (*Hugershoff*, **36**, 3121):

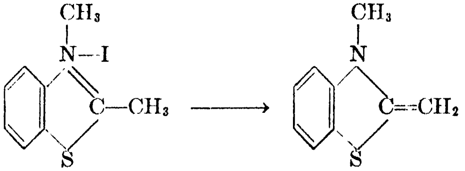


$$NH_2\cdot C\langle\begin{matrix}NC_6H_5\\ SH\end{matrix} \longrightarrow NH_2\cdot C\langle\begin{matrix}N\\ S\end{matrix}\rangle C_6H_4,$$

$$C_6H_5NH\cdot C\langle\begin{matrix}NC_6H_5\\ SH\end{matrix} \longrightarrow C_6H_5NH\cdot C\langle\begin{matrix}N\\ S\end{matrix}\rangle C_6H_4$$

as-Alkylarylthioureas give derivatives of *iminobenzothiazoline* (*Besthorn*, Ber. **43**, 1519).

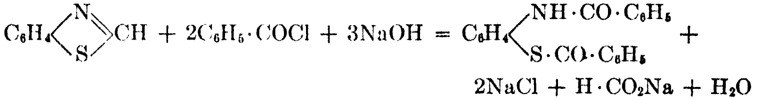
Properties.—The benzothiazoles are slightly basic substances with an odor resembling that of *quinoline*. Many of their reactions are analogous to those of quinoline. When fused with alkali they decompose into aminobenzenethiols and carboxylic acids. At elevated temperatures they form addition products with methyl iodide.



The hydrogen atoms of the 2-methylbenzothiazolium salts are very reactive; the condensation products with aldehydes give dyestuffs of the thioflavine group (*König*, Ber. **61**, 2065; *Schuloff*, *Pollak*, *Riesz*, Ber. **61**, 2538).

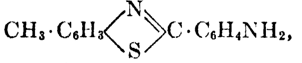
Several benzothiazole derivatives are important as *substantive cotton dyes*.

BENZOTHIAZOLE, *methenylaminothiophenol*, b.p. 234°, is prepared: (*1*) from *o*-aminobenzenethiol and formic acid; (*2*) from formanilide and sulfur; (*3*) from dimethylaniline by heating with sulfur (*cf. Möhlau, Klopfer*, Ber. **31**, 3164); and (*4*) from *o*-nitrophenylthioglycolic acid by heating with concentrated sodium hydroxide (*Friedländer, Chwala*, Mo. **28**, 270). With benzoyl chloride and aqueous sodium hydroxide benzothiazole, similarly to benzimidazole (p. 133), is split into dibenzoyl-*o*-aminobenzenethiol and formic acid (*Reissert*, Ber. **38**, 3430):

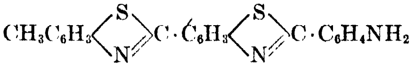


$$C_6H_4\langle\begin{matrix}N\\ S\end{matrix}\rangle CH + 2C_6H_5\cdot COCl + 3NaOH = C_6H_4\langle\begin{matrix}NH\cdot CO\cdot C_6H_5\\ S\cdot CO\cdot C_6H_5\end{matrix} + 2NaCl + H\cdot CO_2Na + H_2O$$

2-Methylbenzothiazole, b.p. 238°; **2-phenylbenzothiazole**, m.p. 114°, also prepared from *o*-aminobenzenethiol and benzaldehyde (*Bogert, Stull*, Am. **47**, 3078). **2-(4′-Aminophenyl)-6-methylbenzothiazole, dehydrothiotoluidine,**

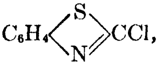
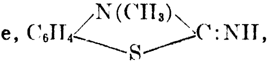


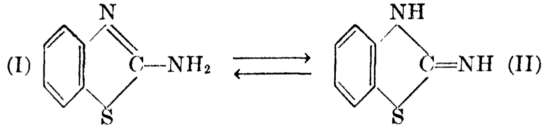
$CH_3\cdot C_6H_3\langle\begin{matrix}N\\ S\end{matrix}\rangle C\cdot C_6H_4NH_2$, m.p. 191°, is obtained from toluidine and aminobenzyl-*p*-toluidine (Ger. Pat. 104230, 1898) by heating with sulfur. Its *trimethylbenzothiazolium chloride* derivative is the dyestuff **thioflavine T.** Further heating with sulfur converts dehydrothiotoluidine to the compound:



$$CH_3C_6H_3\langle\begin{matrix}S\\ N\end{matrix}\rangle C\cdot C_6H_3\langle\begin{matrix}S\\ N\end{matrix}\rangle C\cdot C_6H_4NH_2$$

which is the base of the dyestuff **primuline** (see also *Kym*, Ber. **32**, 3537). This general reaction, heating *p*-methylarylamines with sulfur, produces a series of technically important dyestuffs, which are known as "sulfur dyes" (*v. Weinberg*, Ber. **63**, A117). **2-(4′-Aminophenyl)-5-methylbenzothiazole**, m.p. 218° [*Bogert, Allen*, Ind. Eng.Chem. **18** (1926), 532].

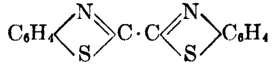
A series of benzothiazole derivatives have been prepared from **2-chlorobenzothiazole**,  $C_6H_4\langle{}^{S}_{N}\rangle CCl$, m.p. 24°, b.p. 248°, which is obtained from phenyl isothiocyanate with PCl_5. 2-Chlorobenzothiazole yields benzothiazole on reduction, 2-benzothiazolol with alcohol, 2-ethoxybenzothiazole with sodium ethylate, 2-mercaptobenzothiazole with NaSH, 2-aminobenzothiazole with NH_3, and 2-anilinobenzothiazole with $C_6H_5NH_2$. **2-Benzothiazolol**, m.p. 136°, is also prepared from chloroformic acid ester with aminobenzenethiol. **2-Ethoxybenzothiazole**, m.p. 25°, b.p. over 360°, is also formed from phenylthiourethan (Vol. III, p. 94) by oxidation with potassium ferricyanide. **2-Benzothiazolethiol**, $C_6H_4(NSC{\cdot}SH)$, m.p. 179°, is also obtained from aminobenzenethiol with CS_2, from azobenzene with CS_2 and from phenyl isothiocyanate with S (*Jacobson, Frankenbacher*, Ber. **24**, 1403). **2-Aminobenzothiazole**, $C_6H_4(NSC{\cdot}NH_2)$, m.p. 129°, and **2-anilinobenzothiazole**, m.p. 159°, are also formed from phenyl- and *s*-diphenylthiourea with bromine in chloroform (see p. 144); when an excess of bromine is present perbromides are produced first (*Hunter, Styles*, J. **1927**, 1209), which are reduced by SO_2 to benzothiazole [*Hunter*, J. **127**, 2023]. 2-Aminobenzothiazole is also prepared by heating β-phenylthiosemicarbazide with hydrochloric acid (*Hugershoff*, Ber. **36**, 3134) and by treating benzothiazole with hydroxylamine (*Skraup*, Ann. **419**, 1); the anilinobenzothiazole is obtained from azobenzene and phenyl isothiocyanate (*Jacobson, Frankenbacher*, Ber. **24**, 1410). The aminobenzothiazole reacts with methyl iodide to give **3-methyl-2-iminobenzothiazoline**,  $C_6H_4\langle{}^{N(CH_3)}_{S}\rangle C{:}NH$, m.p. 123°, which is also formed from *as*-methylphenylthiourea and bromine (*Besthorn*, Ber. **43**, 1519). Often the reactions of 2-aminobenzothiazole (I) can be explained by the assumption that it exists also in the tautomeric form, 2-iminobenzothiazoline (II):



Isomeric perbromides of both forms have been obtained (*Dyson, Hunter, Soyka*, J. **1926**, 2964).

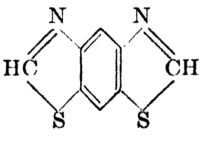
Benzothiazole-2-carboxylic acid melts at 108° while decomposing into CO_2 and benzothiazole; it is formed by oxidation of thioöxanilic acid, $C_6H_5NH{\cdot}CSCOOH$, with potassium ferricyanide in alkaline solution (*Reissert*, Ber. **37**, 3710) and by boiling 2,2-dichloro-3-oxo-dihydro-1,4-benzothiazine with alcohol, whereupon a benzilic acid rearrangement involving a ring-contraction takes place (*Zahn*, Ber. **56**, 578).

When acetanilide is heated with sulfur, **bibenzothiazole** (III) is formed (*Lauth*, C.r. **121**, 1152).

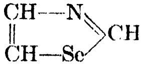
(III)  $C_6H_4\langle{}^{N}_{S}\rangle C{\cdot}C\langle{}^{N}_{S}\rangle C_6H_4$

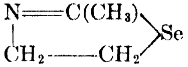
Naphthothiazole (*Jacobson, Klein*, Ber. **26**, 2365), **2-aminonaphthothiazole** (U. S. Pat. 1926932, 1933), **benzo[1,2,5,4]*bis*-thiazole** (IV) (*Bogert, Abrahamson*, Am. **47**, 826), and **anthrathiazoles** (*Green, Perkin*, J. **83**, 1201; *Ullmann, Junghaus*, Ann. **399**, 345) are also known.

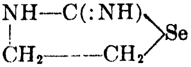
(IV)



The corresponding selenium ring compound, **selenazole** (V) is not itself known, but several derivatives of it have been prepared by methods analogous to those used for the thiazole derivatives. **2-Methylselenazoline** (VI), b.p. 161°, is obtained from *bis*-(acetamidoethyl) diselenide, $(CH_3 \cdot CO \cdot NH \cdot CH_2 \cdot CH_2Se)_2$, with PCl_5; it is an oil having an odor like pyridine (*Michels*, Ber. **25**, 3048). **2-Iminotetrahydroselenazole**, *ethylenepseudoselenourea* (VII), oil, from bromoethylamine and potassium selenocyanide (*Baringer*, Ber. **23**, 1003).

(V)


(VI)


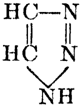
(VII)


III. FIVE-MEMBERED RINGS WITH THREE HETERO ATOMS

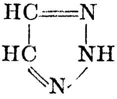
1. TRIAZOLES

The following four groups of triazoles can be divided into two classes:

1. Those with adjacent N-atoms:

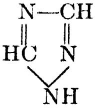


1,2,3-Triazole

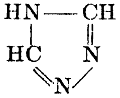


2,1,3-Triazole
(Osotriazole, *v*-triazole)

2. Those with separated N-atoms:

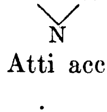


1,2,4-Triazole

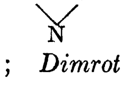


4,1,2-Triazole

When the hydrogen on the N-atom in these compounds is not substituted, the two members of each group are identical. Therefore the hydrogen atom, as in the case of the pyrazoles and the imidazoles, must be attracted equally by all the N-atoms. Instead of the four triazoles shown above, there are only two which exist:

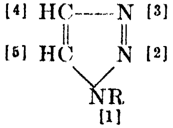


and

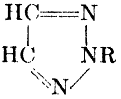


(*Pellizzari*, Atti accad. Lincei [5] **10**, II, 297; *Dimroth*, Ber. **35**, 1038).

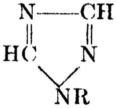
When there is a substituent on a N-atom, the four theoretically possible triazoles can be prepared:



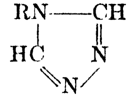
1-Alkyl-1,2,3-triazole



2-Alkyl-2,1,3-triazole

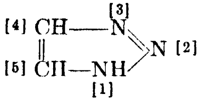


1-Alkyl-1,2,4-triazole

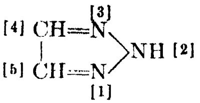


4-Alkyl-4,1,2-triazole

(a) 1,2,3-Triazoles and (b) 2,1,3-Triazoles, Osotriazoles:



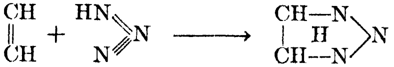
and



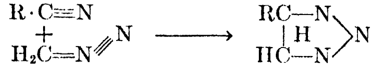
It is not certain from which form the parent compound of these two groups of triazoles and the derivatives without substituents on the nitrogen are derived (see p. 153).

Methods of preparation:

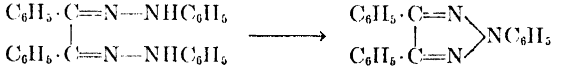
(*1*) By the condensation of hydrazoic acid with acetylene or α-acetylenecarboxylic acids when heated in ethereal solution (*Dimroth*, *Fester*, Ber. **43**, 2219; *Oliveri-Mandalà*, *Coppola*, Atti accad.Lincei [5] **19** (1910), I, 563):



(*2*) By the condensation of diazomethane with certain derivatives of hydrocyanic acid, such as cyanogen chloride, cyanogen bromide, dicyanogen, and cyanoformic ester (*Peratoner*, *Azzarello*, Atti accad.Lincei [5] **16** (1907), II, 237; *Tamburello*, *Millazo*, ibid., 412; *Oliveri-Mandalà*, Gazz. **40**, I, 120):



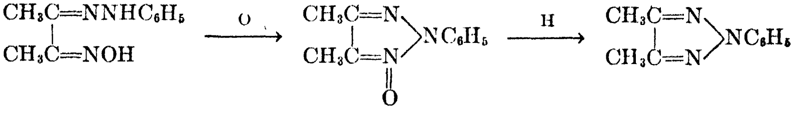
(*3*) Derivatives of 2,1,3-triazole are obtained from the osazones of 1,2-dioxo compounds by boiling with acids or by distillation:



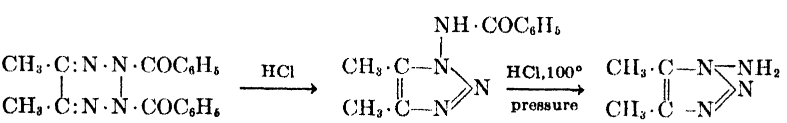
Benzilosazone

2,4,5-Triphenyl-2,1,3-triazole

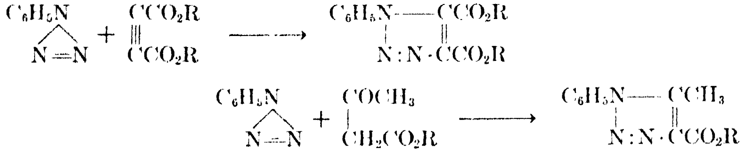
From the hydrazoximes of 1,2-dioxo compounds by elimination of water with acetic anhydride or PCl_5 (Vol. I, p. 409). The α-isonitroso derivatives of ketone methylphenylhydrazones give 2,1,3-triazoles by elimination of methyl alcohol (*Pechmann*, Ann. **262**, 265). If the hydrazoximes are oxidized with N_2O_4 or HgO in chloroform, triazole derivatives containing oxygen are formed first; these are readily converted to 2,1,3-triazoles by reduction or by treatment with PCl_5 (*Ponzio*, J.pr. **57**, 160; Gazz. **38**, II, 522).



(*4*) Derivatives of 1,2,3-triazole are obtained from 2,3-dibenzoyl-5,6-dimethyl-2,3-dihydro-1,2,3,4-tetrazine when heated alone or with hydrochloric acid. After the benzoyl group has been removed from the 1-benzamido-4,5-dimethyl-1,2,3-triazole formed, the 1-amino-4,5-dimethyl-1,2,3-triazole is converted to 4,5-dimethyl-1,2,3-triazole by treatment with nitrous acid (*Pechmann*, *Bauer*, Ber. **42**, 659; *Stollé*, J.pr. **78**, 544; Ber. **59**, 1742):



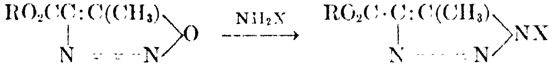
N-Substituted 1,2,3-triazoles are obtained by the reaction of triazobenzene (Vol. III, p. 133) and other esters of hydrazoic acid with α-acetylenecarboxylic acid esters alone or with β-oxo carboxylic acid esters in the presence of sodium alcoholate:



Triazobenzene also adds to malonic esters, cyanoacetic esters, phenylacetic esters, phenylacetonitrile, and to acetic and propionic acid esters and to ketones, to give 5-hydroxy- and 5-amino-1,2,3-triazoles (*Dimroth*, Ber. **35**, 4041; *Dimroth, Frisoni, Marshall*, Ber. **39**, 3920).

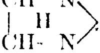
When triazobenzene is boiled with sodium ethylate or homologous alcoholates in alcoholic solution it forms 1-phenyl-1,2,3-triazole or 1-phenyl-4-alkyl-1,2,3-triazoles: $2C_6H_5N_3 + CH_3{\cdot}CH_2ONa = C_6H_5NH_2 + C_6H_5{\cdot}C_2H_2N_3 + NaOH + N_2$; the alcoholate is dehydrogenated to the enolate which reacts with the second triazobenzene molecule (*Bertho*, J.pr. **119**, 173).

By the reaction of hydrazines, semicarbazides, or hydroxylamines with 1,2,3-oxadiazoles (*diazoanhydrides*, p. 165) (*Wolff*, Ann. **325**, 152; *Wolff, Hall*, Ber. **36**, 3612):



By the decomposition of benzotriazoles (azimidobenzenes) substituted on the nitrogen (*Zincke*, Ann. **311**, 276; **313**, 251).

Behavior. 1,2,3- and 2,1,3-Triazoles are mostly weakly basic liquids with an alkaloid-like odor which distill undecomposed. The imine hydrogen is easily replaced by metals. The triazole ring system is very stable, especially to oxidizing agents. Thus, the phenyl group of 2-phenyl-2,1,3-triazole can be split off after amination by simple oxidation, and C-alkyl triazoles are oxidized by $KMnO_4$ to triazolecarboxylic acids. This stability, as well as the diazotizability of the C-amino derivatives, indicate similarity to the aromatic ring systems.

1,2,3-Triazole or 2,1,3-**triazole, osotriazole,** *v*-**triazole,** , m.p. 23°, b.p. 204° (739 mm.), hygroscopic. Silver nitrate precipitates a silver salt, $C_2H_2N_3Ag$, and benzoyl chloride gives the easily decomposed benzoyltriazole, m.p. 100–102°. The triazole is prepared: (*1*) from acetylene and hydrazoic acid; (*2*) from its carboxylic acids (see below) by heating; (*3*) from N-aminotriazole with nitrous acid.

C-Phenyl-1,2,3(or 2,1,3)-**triazole,** m.p. 144°, from its carboxylic acid. **4,5-Dimethyl-** and **4,5-diphenyl-1,2,3** (or 2,1,3)-**triazole,** m.p. 70° and 138°, from the corresponding 2-amino-2,1,3-triazoles with nitrous acid; the first compound is also obtained from 2-phenyl-4,5-dimethyl-2,1,3-triazole.

1-Phenyl-1,2,3-triazole, m.p. 56°, from acetylene and triazobenzene (*Dimroth, Fester*, Ber. **43**, 2222). **1-Phenyl-5-methyl-1,2,3-triazole,** m.p. 64°, and **1,5-diphenyl-1,2,3-triazole,** m.p. 114°, are obtained by heating their carboxylic acid derivatives.

1-Methyl-5-chloro-1,2,3-triazole, liquid, and **1-phenyl-5-chloro-1,2,3-triazole,** m.p. 50°, are prepared from 1-methyl- and 1-phenyl-5-hydroxy-1,2,3-triazolecarboxylic acid esters by treatment with PCl_5, saponification and decarboxylation; the chlorine atom is easily replaced.

1-Phenyl-5-methyl-1,2,3-triazole-4-carboxaldehyde, m.p. 52°; semicarbazone, m.p. 227°. **1,5-Diphenyl-1,2,3-triazole-4-carboxaldehyde,** m.p. 105°; semicarbazone, m.p. 224°; oxime, m.p. 176° (*Rojahn, Trieloff*, Ann. **445**, 296).

2-Methyl-4-chloro-2,1,3-triazole, b.p. 63° (32 mm.), and **2-methyl-4-bromo-2,1,3-triazole,** b.p. 63° (39 mm.), from diazomethane and cyanogen chloride or bromide, explode over 260° (*Tamburello, Millazo*, Atti accad. Lincei [5] **16** (1907), **II**, 412).

2-**Phenyl**-2,1,3-**triazole**, *phenylosotriazole*, b.p. 224°, from its carboxylic acid or from glyoxalosotetrazone; 2-**phenyl**-4-**methyl**-2,1,3-**triazole**, b.p. 150° (60 mm.), from methylglyoxal; 2-**phenyl**-4,5-**dimethyl**-2,1,3-**triazole**, b.p. 192° (60 mm.), from dimethylglyoxal; 2,4,5-**triphenyl**-2,1,3-**triazole**, m.p. 122°, from benzil (*Auwers*, *Meyer*, Ber. **21**, 2806).

2-**Phenyl**-2,1,3-**triazole**-4-**carboxaldehyde**, m.p. 70°, is obtained from its oxime, m.p. 115°, which is the condensation product of the phenylhydrazone of mesoxaldehyde dioxime, $(HON{:}CH)_2C{:}NNH \cdot C_6H_5$; by elimination of water the aldoxime forms 2-**phenyl**-4-**cyano**-2,1,3-**triazole**, m.p. 94°.

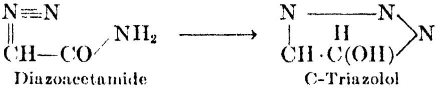
1,2,3(or 2,1,3)-**Triazolecarboxylic acids** are prepared: (*1*) from α-acetylenecarboxylic acids and hydrazoic acid; (*2*) from C-alkyl triazoles by oxidation with permanganate; and (*3*) from N-phenyl-2,1,3-triazole- and 1,2,3-triazolecarboxylic acids by oxidative splitting off of the phenyl group after nitration and reduction.

1,2,3(or 2,1,3)-**Triazolecarboxylic acid**, m.p. 219° (dec.), from propiolic acid and hydrazoic acid, from 2-phenyl-2,1,3-triazole-4-carboxylic acid (see below), from 1-phenyl-1,2,3-triazole-4- and 5-carboxylic acid, and from *Bz*-hydroxytrichlorobenzotriazole by oxidation. Its nitrile, m.p. 114°, is produced in the condensation of dicyanogen with diazomethane (Vol. I, p. 252). 2-**Methyl**-2,1,3-**triazole**-4-**carboxylic acid**, m.p. 142° [*Peratoner*, *Azzarello*, Atti accad. Lincei [5] **16** (1907), II, 237]. C-**Phenyl**-1,2,3 (or 2,1,3)-**triazole**-C-**carboxylic acid**, m.p. 206° (dec.), from phenylpropiolic acid and N_3H. 2-**Phenyl**-2,1,3-**triazole**-4-**carboxylic acid**, m.p. 192°, is prepared by oxidation of 2-phenyl-4-methyl-2,1,3-triazole; when reduced it decomposes to hydrocyanic acid and phenylhydrazinoacetic acid.

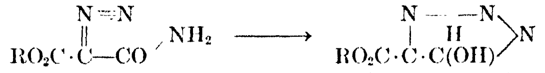
1,2,3(or 2,1,3)-**Triazole**-4,5-**dicarboxylic acid**, m.p. 200°, decomposing into CO_2 and triazole; it is formed from acetylenedicarboxylic acid and N_3H, and by oxidation of benzotriazole and methylbenzotriazole (*Beretta*, Gazz. **55**, 788), of 1-(4′-aminophenyl)-1,2,3-triazoledicarboxylic acid and of C-**methyl**-1,2,3 (or 2,1,3)-**triazole**-C-**carboxylic acid**, m.p. 220° (dec.), whose ester is obtained from acetoacetic ester diazo anhydride (p. 165) by boiling with alcoholic ammonia (*Bladin*, Ber. **26**, 2736). 2-**Phenyl**-2,1,3-**triazole**-4,5-**dicarboxylic acid**, m.p. 236°, from 2-phenyl-4,5-dimethyl-2,1,3-triazole, is readily converted to an anhydride, m.p. 184°.

1-**Phenyl**-5-**methyl**-1,2,3-**triazole**-4-**carboxylic acid**, m.p. 148°, from triazobenzene and acetoacetic ester, is converted by heating to 1-phenyl-5-methyl-1,2,3-triazole, which can be oxidized to 1-**phenyl**-1,2,3-**triazole**-5-**carboxylic acid**, m.p. 176° (dec.). 1-**Phenyl**-1,2,3-**triazole**-4,5-**dicarboxylic acid**, m.p. 150°, is prepared by oxidation of 1-phenyl-5-methyl-1,2,3-triazole-4-carboxylic acid, condensation of acetylenedicarboxylic acid ester with triazobenzene, and oxidation of 1-phenylbenzotriazolequinones; when heated it yields 1-**phenyl**-1,2,3-**triazole**-4-**carboxylic acid**, m.p. 151°.

The C-**hydroxy**-1,2,3(or 2,1,3)-**triazoles** are closely related to the diazocarboxylic acid amides, from which they are obtained by treatment with alkali, or even by fusing or by heating the solutions:



Diazoacetamide C-Triazolol



Diazomalonamic acid ester C-Hydroxytriazole-C-carboxylic acid ester

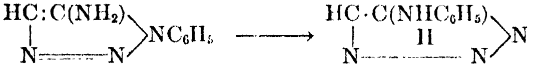
This reaction is reversible, the triazolols being converted more or less completely, by fusion or by warming their solutions to diazocarboxylic acid amides or their decomposition products. The velocity of the isomerization is dependent on the substituents; it takes place readily with the hydroxytriazolecarboxylic acid esters, and most readily with their N-aryl derivatives (*Dimroth*, Ann. **373**, 336).

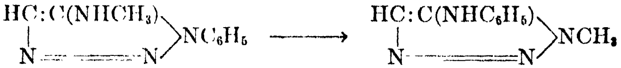
The hydroxytriazoles are strongly acid compounds, which couple with diazonium salts to give hydroxyazo dyes, and react with nitrous acid to form nitrosotriazolols, which may have the structure of isonitrosotriazolones.

C-Triazolol or tautomeric oxo- forms, m.p. 130° (dec.), see p. 149, and from its carboxylic acid ester (see below) by saponification and decarboxylation. It is stable to alkalis, but when boiled with acids it decomposes to nitrogen, ammonia and glycolic acid, probably after preliminary rearrangement to diazoacetamide (*Curtius*, *Bockmühl*, Ber. **43**, 2441). **1-Phenyl-1,2,3-triazol-5-ol**, tautomeric with **1-phenyl-1,2,3-triazol-5-one**, m.p. 119°, from triazobenzene and acetic ester and from its carboxylic acid (see below) by merely warming with water. Permanganate oxidizes it to oxanilic acid, $C_6H_5NH\cdot COCOOH$. Nitrous acid converts it to the unstable yellow **1-phenyl-4-isonitroso-5-triazolone**, dec. 195°, some of whose salts exist in various colored modifications. **1-Phenyl-4-benzoylisonitroso-5-triazolone**, m.p. 133°, rearranges to 2-phenyl-2,1,3,4-tetrazolecarboxylic acid (p. 173) (*Dimroth*, *Dienstbach*, Ber. **41**, 4055). **1-Phenyl-4-methyl-1,2,3-triazol-5-ol**, tautomeric with **1-phenyl-4-methyl-1,2,3-triazol-5-one**, from methylmalonic ester, α-methylacetoacetic ester or propionic acid ester with $C_6H_5N_3$ and sodium alcoholate, is oxidized by $KMnO_4$ to pyruvic acid anilide, $C_6H_5NH\cdot COCOCH_3$. **1,4-Diphenyl-1,2,3-triazol-5-ol**, tautomeric with **1,4-diphenyl-1,2,3-triazol-5-one**, m.p. 151°, from triazobenzene and phenylacetic acid ester.

Methyl C-hydroxytriazole-C-carboxylate or tautomeric forms, m.p. 143°, by heating 1-dinitrophenyl-5-hydroxy-1,2,3-triazolecarboxylic acid ester with alcoholic ammonia. When fused or boiled with alcohol it rearranges in part to diazomalonamic acid ester, from which it can also be formed by the action of sodium ethylate; **amide**, m.p. 196°, from triazobenzene and malonamide by elimination of aniline, is converted by fusion to diazomalonamide, $N_2C(CONH_2)_2$. **1-Methyl-** and **1-phenyl-5-hydroxy-1,2,3-triazole-4-carboxylic acid methyl ester**, tautomeric with **1-methyl-** and **1-phenyl-1,2,3-triazol-5-one-4-carboxylic acid methyl ester**, m.p. 136° and 74°, from triazomethane and triazobenzene and malonic ester (*Dimroth*, Ann. **335**, 1; **338**, 143).

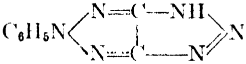
C-Amino-1,2,3(or 2,1,3)-triazoles are prepared by condensation of triazobenzene with cyanoacetic ester and benzyl cyanide and by the reaction of chlorotriazoles with ammonia or amines. The aminotriazoles with unsubstituted nitrogens have acid properties. With nitrous acid they give diazo derivatives which couple in the ordinary way. The C-aminotriazoles, like the C-hydroxytriazoles rearrange readily. **1-Phenyl-5-amino-1,2,3-triazole**, m.p. 110°, from 1-phenyl-5-chloro-1,2,3-triazole with NH_3, rearranges, when fused, to **C-anilino-1,2,3(or 2,1,3)-triazole**, m.p. 139°. Similarly, **1-phenyl-5-methylamino-1,2,3-triazole**, m.p. 102°, when boiled with pyridine isomerizes to **1-methyl-5-anilino-1,2,3-triazole**, m.p. 172°.





Although these rearrangements are not reversible, **1,4-diphenyl-5-amino-1,2,3-triazole**, m.p. 179° (from triazobenzene and benzyl cyanide), and **C-phenyl-C-anilino-1,2,3(or 2,1,3)-triazole**, m.p. 167°, isomerize to an equilibrium mixture containing both compounds when fused or boiled with pyridine. **1-Phenyl-5 amino-1,2,3-triazole-4-carboxylic acid ethyl ester**, m.p. 126°, from triazobenzene and cyanoacetic ester, and **C-anilino-1,2,3(or 2,1,3)-triazole-C-carboxylic acid ethyl ester**, m.p. 130°, form a similar equilibrium mixture. The corresponding acids, m.p. 142° and 153°, yield the same C-anilinotriazole (see above) when decarboxylated by fusion (*Dimroth*, Ann. **364**, 183).

2-Phenyl-4-methyl-5-amino-2,1,3-triazole, m.p. 83°, is formed from the di-(phenylhydrazone) of pyruvic acid amide, $C_6H_5NHN:C(NH_2)\cdot C(CH_3):NNHC_6H_5$ (*Bamberger*, *de Gruyter*, Ber. **26**, 2783; *Jagerspacher*, Ber. **28**, 1283); it forms a diazo derivative which, when boiled with water, gives **2-phenyl-4-methyl-5-hydroxy-2,1,3-triazole**, m.p. 141°, and, when treated with potassium cyanide-copper cyanide, **2-phenyl-4-methyl-5-cyano-2,1,3-triazole.** **2-Phenyl-4,5-diamino-2,1,3-triazole,** m.p. 143°, from the phenylhydrazone of oxamide-oxime, $C_6H_5NH \cdot N{:}C(NH_2) \cdot C(NH_2){:}NOH$, is similar in many respects to the aromatic diamines: with ferric chloride it forms a blue dyestuff of the *azine* type and with *o*-diketones it yields compounds analogous to quinoxaline. It does not form anhydro bases. Nitrous acid converts it to a stable diazo compound which reacts with sodium acetate to form *phenylosotriazoleazimide, 2-phenyl-v-triazolo*[d]-*v-triazole*:

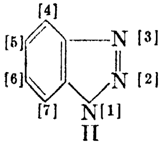


The latter readily decomposes to the diazo compound (cf. *Thiele, Schleussner,* Ann. **295**, 129).

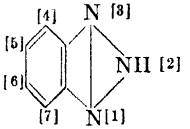
N-Amino- and **N-hydroxy-1,2,3-triazoles. 1-Amino-5-methyl-1,2,3-triazole,** m.p. 70°, from its carboxylic acid, which is prepared from the condensation product of acetoacetic ester diazo anhydride with semicarbazide by saponification (*Wolff, Hall,* Ber. **36**, 3612). **1-Anilino-5-methyl-1,2,3-triazole** and its carboxylic acid are formed from acetoacetic ester diazo anhydride with phenylhydrazine (*Wolff,* Ann. **325**, 156). **1-Hydroxy-5-methyl-1,2,3-triazole-4-carboxylic acid,** dec. 205°, is a dibasic acid; its ester is obtained from acetoacetic ester diazo anhydride with hydroxylamine; oxidation converts it to **1-hydroxy-1,2,3-triazole-4,5-dicarboxylic acid,** which is also formed by oxidation of 1-hydroxybenzotriazole (p. 152) (*Wolff,* Ann. **325**, 162).

(c) Benzotriazoles

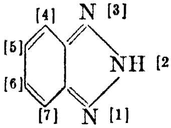
The bicyclic ring system of benzotriazole consists of a benzene ring and a 1,2,3- or 2,1,3-triazole ring (p. 147) having two adjacent carbon atoms in common. The difficulty in assigning a single structural formula to N-unsubstituted triazoles (p. 147, 153) is carried over to the N-unsubstituted benzotriazoles. For the parent compound the following three formulas are possible:



I (Also azimidobenzene)

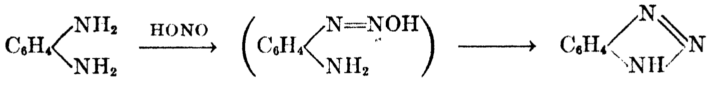


II (Also pseudo-azimidobenzene)



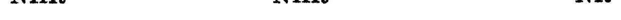
III

(*1*) N-Unsubstituted benzotriazoles are prepared from aromatic *o*-diamines and nitrous acid:



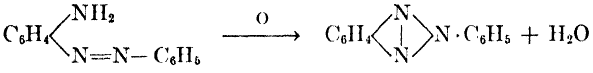
Benzotriazole, *azimidobenzene,* m.p. 98°, isomeric with triazobenzene. **5(6)-Methylbenzotriazole,** *azimidotoluene,* m.p. 83–84°, from toluenediamine by the same method. *Platinum chloride double salt* (*Noelting, Abt,* Ber. **20**, 3001).

(*2*) N-Substituted benzotriazoles can be obtained according to method (*1*) if monoalkyl-*o*-diamines are reacted with nitrous acid. From their method of preparation the compounds so formed must be derived from formula I (*Bietzki, Raillard,* Ber. **31**, 1460):

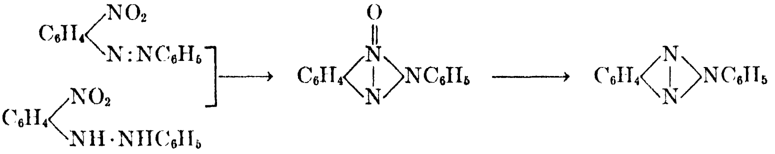


When there is one substituent on the benzene ring, this reaction produces two isomers (*Zincke, Helmert*, J.pr. **53**, 95), which is added evidence that they are derived from 1-benzotriazole (formula I).

(*3a*) N-Aryl-benzotriazoles derived from formula II or III (pseudoazimidobenzene) are prepared from *o*-aminoazo compounds by oxidation with chromic acid in acetic acid solution (*Kehrmann, Messinger*, Ber. **25**, 901; *Witt, Schmidt*, Ber. **27**, 2374; *Witt*, Ber. **45**, 2383) or, in many cases, merely by heating in high-boiling (over 155°) solvents in the presence of copper powder (*Crippa*, Gazz. **55**, 706):



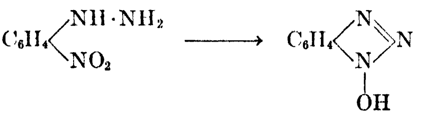
(*3b*) N-Arylbenzotriazoles of the same type are formed by careful reduction of *o*-nitroazo- or *o*-nitrohydrazo compounds with sodium sulfide or sodium hydrosulfite (*Willgerodt, Klein*, J.pr. **60**, 104; *Werner, Stiasny*, Ber. **32**, 3266). The intermediate products thus formed are converted to benzotriazoles by stronger reduction with $SnCl_2$ and HCl [*Bamberger, Hübner*, Ber. **36**, 3822; *cf. Chakravarty, Dutt*, J.Indian Chem.Soc. **5** (1929), 555]:



Properties.—In behavior benzotriazole resembles naphthalene. Benzotriazoles substituted in the 5(6)-position behave like 2-substituted naphthalenes in bromination, nitration and coupling with diazonium salts (*Fries, Sudhoff, Brettschneider*, Ann. **454**, 121). The benzotriazoles are very resistant to hydrolyzing agents (mineral acids) even at high temperatures. Most of them can be distilled at atmospheric pressure without decomposition. Strong oxidation destroys the benzene ring, leaving triazoledicarboxylic acids. The benzotriazoles with no substituents on the nitrogen are decidedly acid, forming salts with sodium hydroxide and other metal hydroxides. By means of these salts a series of alkyl groups can be substituted on the nitrogen. The N-substituted benzotriazoles add one molecular proportion of alkyl halide, forming quaternary benzothiazolium compounds.

1-Phenyl-6-ethoxybenzotriazole, m.p. 108°, is isomeric with **1-phenyl-5-ethoxybenzotriazole**, m.p. 99° (*Zincke, Hilmert*, J.pr. **53**, 97). **1-Tolyl-6-methylbenzotriazole**, m.p. 95°, from *o*-aminoditolylamine (*Täuber*, Ber. **25**, 1023). Its isomer, **2-tolyl-5-methylbenzotriazole**, m.p. 126° (*Zincke*, Ber. **18**, 3143). **2-Phenylbenzotriazole**, m.p. 109°, from *o*-aminoazobenzene by method *2* (p. 151). For the oxidative degradation of these benzotriazoles to *triazole*-4,5-*dicarboxylic acids* (p. 149), see *Zincke, Petermann*, J.pr. **58**, 244.

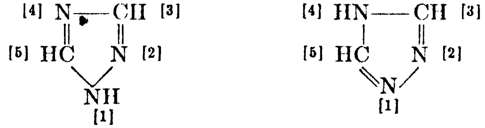
1-Hydroxybenzotriazoles, the benzazimidols, are obtained from *o*-nitrophenylhydrazines with alkali:



1-Benzotriazolol, *benzazimidol*, m.p. 157°, is a rather strong acid; reduction with HI gives benzotriazole, and oxidation yields 1-hydroxy-1,2,3-triazole-4,5-dicarboxylic acid.

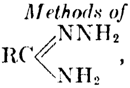
NAPHTHOTRIAZOLES have also been prepared; *cf. Noelting, Grandmougin, Freimann*, Ber. **42**, 1380; *Charrier*, Atti accad.Lincei [6] **4** (1927), 312. For **acenaphthotriazoles**, see *Charrier, Beretta*, Gazz. **55**, 745.

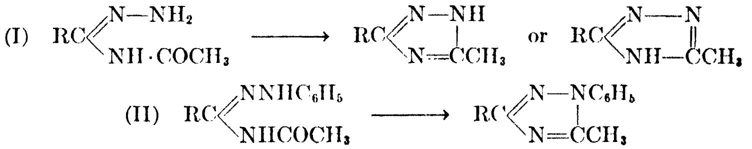
(d) 1,2,4-Triazoles and (e) 4,1,2-Triazoles



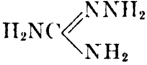
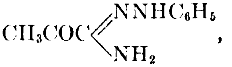
(also called *s*-triazoles)

It is not certain from which form the parent compound of these two groups of triazoles and the derivatives without substituents on the nitrogen are derived (see p. 147). The structure of the N-phenyl derivatives is apparent from their synthesis.

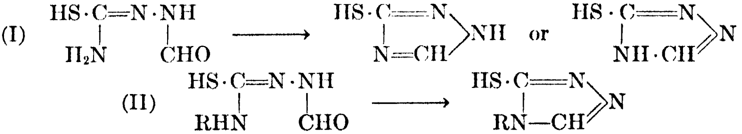
Methods of Preparation.— (*1*) *Hydrazidines* or *amidrazones* (Vol. III, p. 310),

$RC\left\langle\begin{matrix}NNH_2\\NH_2\end{matrix}\right.$, are converted by carboxylic acid anhydrides to acyl derivatives which condense to triazoles by elimination of water:



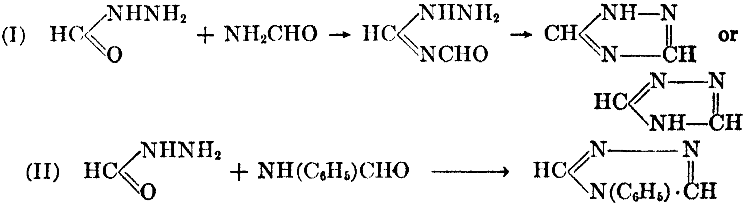
The hydrazidines react similarly with aldehydes and ketones.

In this way triazoles were first prepared by *Bladin* (Ber. **18**, 1544; **25**, 183) from acid derivatives of the phenylhydrazone of *cyanoformamide*, $CN\cdot C(NH_2)$:-$NNHC_6H_5$; compounds such as *aminoguanidine*,

$H_2NC\left\langle\begin{matrix}NNH_2\\NH_2\end{matrix}\right.$, and *α-amino-α-phenylhydrazonoacetone*,

$CH_3COC\left\langle\begin{matrix}NNHC_6H_5\\NH_2\end{matrix}\right.$, condense similarly (*Thiele, Heidenreich*, Ber. **26**, 2598; *Pinner*, Ber. **27**, 989; *Pinner, Caro*, Ber. **27**, 3273; *Thiele, Manchot*, Ann. **303**, 33).

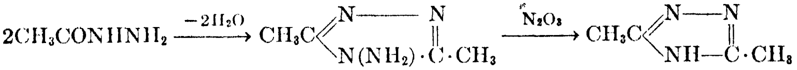
(*2*) *Acylthiosemicarbazides*, $HS\cdot C(NH_2):NNHCOR$, are converted to triazolethiols when heated over their melting points; the mercaptans can be oxidized to triazoles [*Freund*, Ber. **29**, 2483; *Johnson, Menge*, Am.Chem.J. **32** (1904), 1505]:



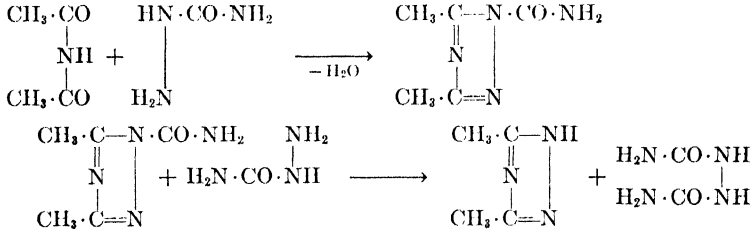
(*3*) When *acid amides* are heated with *acid hydrazides*, or, more simply, acid amides (2 mols) with hydrazine hydrochloride (1 mol), triazoles are obtained, apparently after intermediate formation of acylhydrazidines (*Pellizzari*, Gazz. **24**, II, 222; *Pellizzari, Massa*, Gazz. **26**, II, 413):



Mono- and diacylhydrazines when heated alone yield N-aminotriazoles, which lose the amino group as nitrous oxide on treatment with nitrous acid:

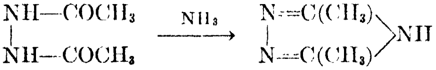


(*4*) Under very mild conditions *s*-triazoles are formed by the action of diacetamide or its homologues on semicarbazide hydrochloride in aqueous solution in the presence of sodium acetate (*Brunner*, Mo. **36**, 509; reaction mechanism: *Brunner, Medweth*, Mo. **47**, 741). The synthesis follows this course:

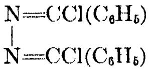


This method can also be used for N-substituted 1,2,4-triazoles, since phenylhydrazine hydrochloride can be used for the hydrazine component.

(*5*) Triazoles are synthesized from *s-diacylhydrazines* and zinc ammonium chloride or primary amines; see the analogous syntheses of 1,3,4-oxadiazoles and thiadiazoles (pp. 163, 166) and the general equation for azole syntheses (p. 90) (*Stollé*, Ber. **32**, 797; *Busch, Schneider*, J.pr. **89**, 319; *Heller*, J.pr. **120**, 52):



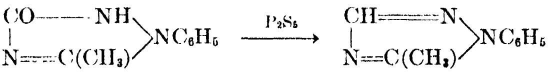
Closely related to this reaction is that of hydrazide chlorides:



$$\begin{array}{l} N{=}CCl(C_6H_5) \\ | \\ N{=}CCl(C_6H_5) \end{array}$$

with ammonia and primary amines, which takes place at lower temperatures (*Stollé*, J.pr. **73**, 278).

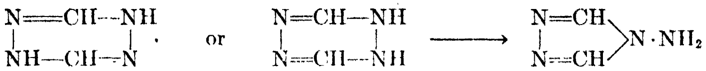
(*6*) Triazoles are obtained from triazolones and urazoles (p. 158) by distillation with P_2S_5; triazole derivatives containing sulfur are formed as intermediate products (*Andreocci*, Ber. **25**, 225; *Pellizzari, Cuneo*, Ann.chim.farm. **1894**, 260; *Pellizzari, Ferro*, Gazz. **28**, II, 541):



Phenylmethyltriazolone **1-Phenyl-5-methyltriazole**

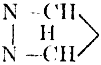
Triazolones and PCl_5 give chlorotriazoles, which are converted to triazoles by reduction.

(*7*) N-Aminotriazoles are formed by rearrangement of N-dihydrotetrazines:



With dihydrotetrazine itself, this rearrangement takes place on fusion, but in other cases heating with aqueous or alcoholic hydrochloric acid or concentrated aqueous alkali is necessary.

Behavior.—The 1,2,4- and 4,1,2-triazoles are, like the other triazoles, only slightly basic (*Dedichen*, Ber. **39**, 1849). The platinum chloride double salts behave like those of the pyrazoles (p. 92; *Pellizzari*, *Massa*, Gazz. **26**, II, 417). The imine hydrogen can be replaced by metals. C-Alkyl-1,2,4- or -4,1,2-triazoles oxidize to triazolecarboxylic acids; the ring is resistant to oxidation. The phenyl group in the N-phenyltriazoles, especially after amination, can be removed by oxidation.

1,2,4(or 4,1,2)-**TRIAZOLE**, *s*-**triazole**,  $\begin{matrix} N-CH \\ \vert \quad H \\ N-CH \end{matrix}\!\!>\!N$, m.p. 121°, b.p. 260°, is a weak base; its platinum double salt, $(C_2H_3N_3.HCl)_2PtCl_4$, loses 2HCl when heated; nitrate, m.p. 138°; copper salt, $(C_2H_2N_3)_2Cu$, from a solution of triazole with copper sulfate. The *s*-triazole is prepared: (*1*) from formamide and formic acid hydrazide; (*2*) from urazole (p. 158) with P_2S_5; (*3*) from N-aminotriazole with N_2O_3; (*4*) from its carboxylic acid (*Thiele*, *Manchot*, Ann. **303**, 55); (*5*) from triazolethiol by oxidation with H_2O_2 (*Freund*, Ber. **29**, 2485); and (*6*) from 1-phenyl-1,2,4-triazole and from 4-phenyl-4,1,2-triazole by oxidative removal of the phenyl group.(*Pellizzari*, Atti accad.Lincei [5] **10**, II, 297).

C-Methyltriazole, m.p. 94°, from 1-phenyl-3-methyl-1,2,4-triazole by removal of the phenyl group (*Andreocci*, Ber. **25**, 225). **C-Phenyltriazole**, m.p. 116°, by reduction of N-phenylbromotriazole with sodium amalgam (*Manchot*, Ber. **43**, 1315). 3,5-**Dimethyltriazole**, m.p. 142°, b.p. 159° (19 mm.) (by method *4*, p. 154). 3,5-**Diethyltriazole**, m.p. 66°, b.p. 267°, from semicarbazide hydrochloride and dipropionamide (*Grüner*, *Benes*, *Schubert*, *Arman*, Mo. **48**, 37). 3,5-**Diphenyltriazole**, m.p. 192°, from semicarbazide hydrochloride and dibenzamide (*Wolchowe*, Mo. **37**, 476), and 3,5-**difuryltriazole**, m.p. 185°, are also prepared from the corresponding N-aminotriazoles by methods *1* and *5*. The 3,5-diphenyltriazole is also formed by the action of acids on benzal-α-isonitrosobenzylhydrazine, $C_6H_5C(:NOH)NH\cdot N:CHC_6H_5$ (*Wieland*, Ber. **42**, 4200) and from C-phenyltetrazole (p. **172**) by heating.

4-**Phenyl**-4,1,2-**triazole**, m.p. 121°, from formic acid hydrazide and formanilide (Vol. III, p. 88), has a physiological action similar to strychnine (*Pellizzari*, *Massa*, Atti accad.Lincei [5] **10**, I, 363). 4-**Methyl**-4,1,2-**triazole**, m.p. 121°, from formic acid hydrazide and methyl formamide, and from its mercaptan with H_2O_2 (see below). 3,4-**Diphenyl**-4,1,2-**triazole**, m.p. 142°, from its mercaptan (*Marckwald*, *Bott*, Ber. 29, 2919). 3,4,5-**Triphenyl**-4,1,2-**triazole**, m.p. 292°, from dibenzoylhydrazine chloride (Vol. III, p. 307) and aniline.

1-**Methyl**-1,2,4-**triazole**, m.p. 20°, b.p. 183°, from the sodium salt of 1,2,4-triazole and methyl iodide, and from formylmethylhydrazine and formamide (*Pellizzari*, *Soldi*, Gazz. **35**, I, 373). **1-Phenyl**-1,2,4-**triazole**, m.p. 47°, b.p. 266°, from its carboxylic acid (p. **157**). 1-**Phenyl-5-methyl**-1,2,4-**triazole**, m.p. 191°, from its carboxylic acid. 1-**Phenyl**-3-**methyl**-1,2,4-**triazole**, m.p. 87°, b.p. 274°, from phenylmethyltriazolone with P_2S_5 (for its formation from benzeneazoacetaldoxime N-methyl ether, Vol. III, p. 163, by elimination of water, see *Bamberger*, *Frei*, Ber. **35**, 752). 1,3-**Diphenyl**-1,2,4-**triazole**, m.p. 97°, from formylbenzamide, $C_6H_5CONH\cdot CHO$, and phenylhydrazine (*Einhorn*, Ann. **343**, 229). 1,5-**Diphenyl**-1,2,4-**triazole**, m.p. 91°, from 1,5-diphenyl-3-chlorotriazole with hydriodic acid and phosphorus. 1,3,5-**Triphenyl**-1,2,4-**triazole**, m.p. 104°, from benzonitrile (2 mols), phenylhydrazine (1 mol) and sodium; in this reaction a hydrazidine, $C_6H_5C(NH)N(C_6H_5)\cdot N:C(NH_2)C_6H_5$, is apparently formed first. Substituted phenylhydrazines and benzonitrile react similarly (*Walther*, *Krumbiegel*, J.pr. **67**, 481). The triphenyltriazole is also obtained from dibenzamide and phenylhydrazine hydrochloride (method *4*, p. 154, and *Wolchowe*, Mo. **37**, 479). 1-**Phenyl**-3,5-**diethyl**-1,2,4-**triazole**, m.p. 38°, and other 3,5-dialkyltriazoles: *Grüner*, *Benes*, *Schubert*, *Arman*, Mo. **48**, 37.

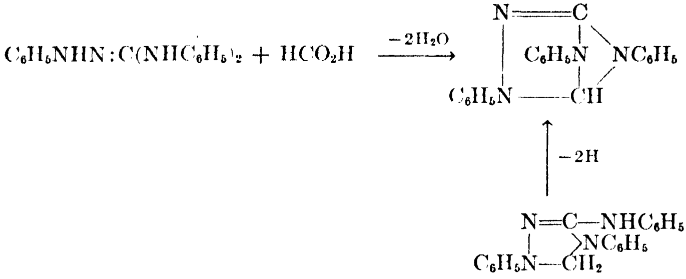
HALOGEN DERIVATIVES of 1,2,4(or 4,1,2)-triazoles are prepared by heating triazolones with PCl_5 and $POCl_3$ at elevated temperatures and by the action of hydrogen halide acids on the diazo compounds of amino-1,2,4(or 4,1,2)-triazoles. The halogen is bound as firmly as in chlorobenzene, and is removed only by treatment with HI and P. **C-Chloro-**, **C-bromo-**, **C-iodo-*s*-triazole**, m.p. 167°, 189°, and 208°, and **C,C-methylchloro-*s*-triazole**, m.p. 147°, from the diazo compounds of the corresponding aminotriazoles (*Manchot*, *Noll*, Ann. **343**, 9). **1-Phenyl-5-chloro-*s*-triazole**, m.p. 54°. **1,5-Diphenyl-3-chloro-*s*-triazole**, m.p. 96°. **1-Phenyl-3,5-dichloro-*s*-triazole**, m.p. 94° [*Cleve*, Ber. **29**, 2671; *Andreocci*, Atti accad.Lincei [5] **6** (1897), 217].

For **hydroxy-s-triazoles**, see under triazolones.

TRIAZOLETHIOLS, from acylthiosemicarbazides (method *2*), are converted by mild oxidation to disulfides and by strong oxidation to triazoles. **Triazole-3-thiol**, m.p. 216°; **4-methyl-** and **4-ethyl-4,1,2-triazole-3-thiol**, m.p. 168° and 97° [*Freund*, Ber. **29**, 2484; *Johnson*, *Menge*, Am.Chem.J. **32** (1904), 358].

3-**AMINO**-1,2,4(or 4,1,2)-**TRIAZOLES** are synthesized from acyl derivatives of aminoguanidine, $NH_2C(:NH)NHNHCOR$ (Vol. I, p. 515). They form diazo derivatives which couple with amines and phenols to give dyestuffs, reduce to triazolehydrazines, oxidize to azotriazoles and give halogenotriazoles when treated with hydrogen halide acids (*Manchot*, *Noll*, Ann. **343**, 1). 3-**Aminotriazole**, m.p. 159°, from formylaminoguanidine and from aminotriazolecarboxylic acid; 3-**amino-5-methyltriazole**, m.p. 148° (*Thiele*, *Manchot*, Ann. **303**, 33). 3-**Amino-1-phenyl-1,2,4-triazole**, m.p. 150° (*Cuneo*, Gazz. 22, I, 12).

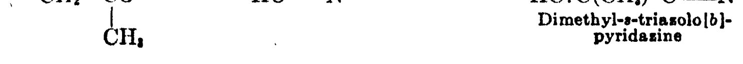
3-**Anilino-4-phenyl-4,1,2-triazole**, m.p. 213°, is prepared from aminodiphenylguanidine and formic acid (*Busch*, *Bauer*, Ber. **33**, 1067). **1,4-Diphenyl-3-anilinodihydrotriazole** (see below), m.p. 128°, from anilinodiphenylguanidine and formaldehyde, and its homologues are converted by gentle oxidation to *endoiminodihydrotriazoles*, 2,3,5,6-tetrazabicyclo[2.1.1]-3-hexenes, which are also obtained directly by condensation of arylaminodiarylguanidines with carboxylic acids or their chlorides:



The endoiminodihydrotriazoles are yellow compounds with strongly basic properties which are readily split into their original components by caustic alkalis (*Busch*, Ber. **38**, 856; *Busch*, *Mehrtens*, Ber. **38**, 4049). The nitrates of the endoiminodihydrotriazoles are very sparingly soluble; **triphenylendoiminodihydrotriazole** (see above), m.p. 189°, known as *nitron*, is used for the detection and gravimetric determination of nitric acid (*Busch*, Ber. 38, 861).

Similarly condensation of carboxylic acids and their chlorides with diarylsemicarbazides and diaryl thiosemicarbazides produces *endoöxydihydrotriazoles* (5-oxa-2,3,6-triazabicyclo[2.1.1]-3-hexenes) or *endothiodihydrotriazoles* (5-thia-2,3,6-triazabicyclo[2.1.1]-3-hexenes) (*Busch*, J.pr. **67**, 201).

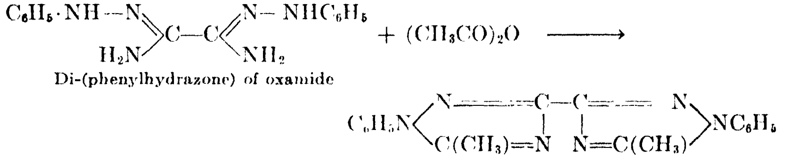
4-**AMINO**-4,1,2-**TRIAZOLES** are prepared by heating mono- and diacylhydrazines and by rearrangement of N-dihydrotetrazines (p. 154). **4-Amino-4,1,2-triazole**, m.p. 83°, by heating formylhydrazine to 210–220°, by fusion of N-dihydrotetrazine and its carboxylic acids and by decarboxylation of 4-aminotriazoledicarboxylic acid (see below) (*Curtius*, *Darapsky*, *Müller*, Ber. **41**, 3168). **4-Amino-3,5-dimethyl-**, **-diethyl-** and **-diphenyl-4,1,2-triazole**, m.p. 199°, 167° and 258°. 4-Aminodimethyltriazole is also obtained from acetohydroxamic acid chloride and hydrazine (*Wieland*, Ber. **40**, 1677). The amino group in 4-amino-4,1,2-triazoles is split off as nitrous oxide by the action of nitrous acid. The N-aminotriazoles condense with aldehydes and ketones like substituted hydrazines, with elimination of water: 4-benzylideneamino-4,1,2-triazole, $C_6H_5CH:N\cdot N_3C_2H_2$, m.p. 170°. With 1,3-diketones and β-oxo carboxylic acid esters bicyclic compounds containing a triazole and a pyridazine ring are formed (*Bülow*, Ber. **42**, 2594):



Dimethyl-s-triazolo[b]-pyridazine

TRIAZOLECARBOXYLIC ACIDS. **Triazole-3-carboxylic acid,** m.p. 137° (dec.), by oxidation of 3-methyltriazole and of 1-aminophenyl-1,2,4-triazole-3-carboxylic acid with $KMnO_4$. **1-Phenyl-1,2,4-triazole-3-carboxylic acid,** m.p. 184°, from 1-phenyl-3-methyl-1,2,4-triazole, and by decarboxylation of 1-phenyl-1,2,4-triazole-3,5-dicarboxylic acid, which is obtained by oxidation of 1-**phenyl-5-methyl-1,2,4-triazole-3-carboxylic acid,** m.p. 177°; the latter is formed by saponification of its nitrile, **1-phenyl-5-methyl-3-cyanotriazole,** m.p. 109° (from dicyanophenylhydrazine with acetic anhydride), or by controlled oxidation of **1-phenyl-5-methyl-3-acetyltriazole,** m.p. 89° (from α-amino-α-phenylhydrazonoacetone) with acetic anhydride. **5-Amino-1,2,4(or 4,1,2)-triazole-3-carboxylic acid,** m.p. 182° (with loss of CO_2), is prepared from oxalylaminoguanidine and, together with **4-amino-4,1,2-triazole-4,5-dicarboxylic acid,** m.p. 77° (dec.), by warming N-dihydrotetrazinedicarboxylic acid with concentrated potassium hydroxide solution; it forms a *diazotriazolecarboxylic acid* which loses nitrogen when warmed with alcohol to give triazole (*Thiele, Manchot,* Ann. **303,** 51; *Curtius, Darapsky, Müller,* Ber. **40,** 1194).

3,3′-BI-*s*-TRIAZOLES are produced by the reaction of the dihydrazone and the di-(phenylhydrazone) of oxamide (*Bamberger, de Gruyter,* Ber. **26,** 2389) with acids or their anhydrides (*Bladin,* Ber. **21,** 3063; *Rinman,* Ber. **30,** 1194):

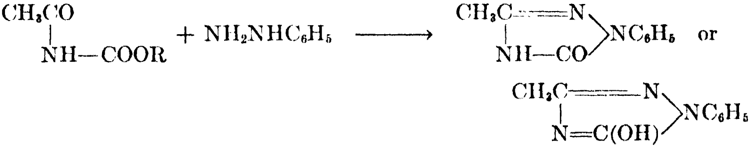

Di-(phenylhydrazone) of oxamide

1,1′-Diphenyl-5,5′-dimethyl-3,3′-bi-1,2,4-triazole

Bi-*s*-triazole, $(C_2H_2N_3)_2$, from the dihydrazone of oxamide and formic acid, sublimes over 300°.

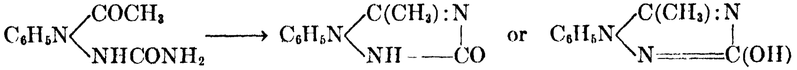
TRIAZOLONES, oxo derivatives of dihydrotriazoles, which also react in the tautomeric form as hydroxytriazoles [*cf.* pyrazolones, p. 97, and *Andreocci,* Atti accad.Lincei [5] **6** (1897), I, 378], are prepared:

(*1*) From acetylurethan and phenylhydrazines:

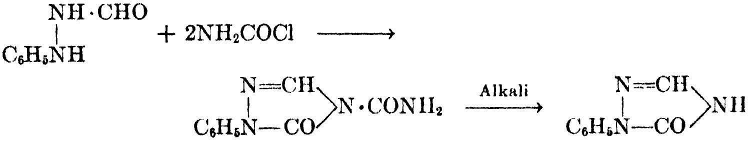


This reaction corresponds to the formation of phenylmethylpyrazolone from acetoacetic ester and phenylhydrazine.

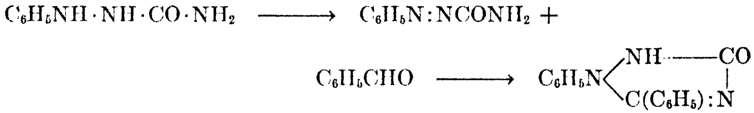
(*2*) From acid derivatives of phenylsemicarbazide by warming with dilute aqueous alkali (*Widman,* Ber. **29,** 1946; *Widman, Cleve,* Ber. **31,** 378):



(*3*) Carbamic acid derivatives of triazolones or hydroxytriazoles are obtained by the action of *s*-acylphenylhydrazines on carbamic acid chlorides. This reaction does not take place with benzoylphenylhydrazine, but does with hexahydrobenzoylphenylhydrazine (*Rupe, Metz,* Ber. **36,** 1092):

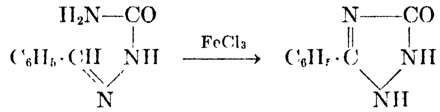


(*4*) Triazolones are formed by the condensation of aldehydes with semicarbazides in the presence of an oxidizing agent, or with azoformamides (*Young, Stockwell*, J. **73**, 368; *Young, Witham*, J. **77**, 224):



Properties.—The triazolones usually react as acids, in the form of triazolols; with P_2S_5 they give triazoles, and with PCl_5, chlorotriazoles.

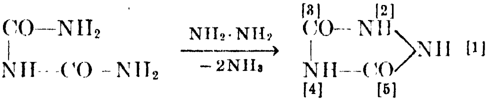
1,2,4-Triazolone, tautomeric with 1,2,4(or 4,1,2)-*triazolol*, m.p. 234°, is obtained from acetone semicarbazone and formic acid, and from hydroxytriazolecarboxylic acid, which is prepared from diazotriazolecarboxylic acid (p. 157) with dilute sulfuric acid (*Manchot*, Ber. **31**, 2444); it reacts as an acid. **1-Phenyl-1,2,4-triazol-3(2)-one**, from phenylsemicarbazide and formic acid, sublimes and melts at 274°. C-Alkyl- or aryl-triazolones result from oxidation of the corresponding aldehyde semicarbazones with alcoholic ferric chloride in a closed tube (*Backer, Mulder*, Rec. **44**, 1113):



1-Phenyl-1,2,4-triazol-5(4)-one, m.p. 183°, is prepared from formylphenylhydrazine with carbamic acid chloride and from its carboxylic acid, **1-phenyl-5-triazolone-3-carboxylic acid**, which is formed from **1-phenyl-3-methyl-5-triazolone**, m.p. 167°, b.p. over 300°, by oxidation with $KMnO_4$ (*Andreocci*, Atti accad. Lincei **1890**, II, 209); the latter is also obtained from acetylphenylhydrazine with $NH_2 \cdot COCl$. **C-Phenyltriazolone**, $C_6H_5C{:}N \cdot NH \cdot CO \cdot NH$ or $C_6H_5C{:}N \cdot CONH \cdot NH$, m.p. 322°, is prepared by heating benzalsemicarbazide with ferric chloride in alcoholic solution (*Backer, Mulder*, Rec. **44**, 1113).

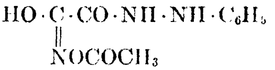
THIOTRIAZOLONES are formed from acylthiosemicarbazides by boiling with dilute alkali. **3,4-Diphenyl-4,1,2-triazole-5(4)-thione**, m.p. 287°, from 1-benzoyl-4-phenylthiosemicarbazide, $C_6H_5 \cdot CO \cdot NH \cdot NH \cdot CS \cdot NH \cdot C_6H_5$. Other triazolethiones are obtained similarly (*Fromm, Trnka*, Ann. **442**, 150).

URAZOLES, or **dioxotetrahydrotriazoles**, are prepared by heating urea and urea derivatives, such as allophanic acid and biuret, with hydrazine salts:



Biuret Urazole

Urazole, *triazolidine*-3,5-*dione*, or the tautomeric enol forms, m.p. 244°, is formed from hydrazoformamide, $NH_2 \cdot CO \cdot NH \cdot NH \cdot CO \cdot NH_2$, by heating over the melting point (*Thiele, Stange*, Ann. **283**, 16), biuret (*Pellizzari, Cuneo*, Gazz. **24, I**, 506), aminobiuret (*Thiele, Uhlfelder*, Ann. **303**, 101), and diaminobiuret. Urazole is a strong monobasic acid; when distilled with P_2S_5 it yields triazole. For the conversion of urazole to tetraacetylhydrazine by heating with acetic anhydride and sodium acetate, see *Cuneo*, Ann.chim.farm. **26** (1898), 481. **1-Phenylurazole**, $C_6H_5N \cdot NH \cdot CO \cdot NH \cdot CO$ (or the tautomeric enol forms) (*Acree*, Ber. **36**, 3139; *Acree, et al.*, Ber. **41**, 3199), m.p. 263°, is obtained from urea and phenylhydrazine, from phenylsemicarbazidocarboxylic acid ester (*Rupe*, Ber. **29**, 829; *Acree*, Ber. **37**, 618) and from the acetyl derivative of oxalohydroxamic acid phenylhydrazide:



$$\begin{array}{l} HO\cdot C\cdot CO\cdot NH\cdot NH\cdot C_6H_5 \\ \quad \| \\ \quad NOCOCH_3 \end{array}$$

by a Beckmann rearrangement (*Thiele, Schleussner*, Ann. **295**, 136). With methyl iodide it gives **dimethylphenylurazole**, m.p. 95°. The isomeric **4-phenylurazole**, $C_6H_5N\cdot CO\cdot NH\cdot NH\cdot CO$, m.p. 203°, is prepared from hydrazoformamide with aniline hydrochloride.

The **4-aminourazoles**, sometimes called *urazines*, are formed by condensation of hydrazine derivatives of carbonic acid (*Busch*, Ber. **40**, 2093). **4-Aminourazole**, m.p. 270°, is prepared from hydrazoformic acid ester and hydrazine hydrate at 110°. **1-Phenyl-4-aminourazole**, m.p. 245°, from phenylhydrazoformic acid ester chloride, $C_6H_5N(COCl)NHCOOR$, and hydrazine; with nitrous acid it gives 1-phenylurazole (*Busch, Heinrichs*, Ber. **33**, 455). **1-Phenyl-4-anilinourazole**, m.p. 264° (*Rupe, Gebhardt*, Ber. **32**, 16).

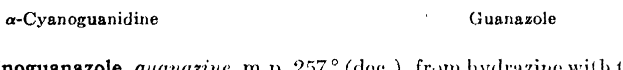
3-Thiourazole, $NH\cdot NH\cdot CS\cdot NH\cdot CO$ (or tautomeric forms), m.p. 206°, from 1-methylmercaptoformylthiosemicarbazide, $CH_3S\cdot CO\cdot NH\cdot NH\cdot CSNH_2$, by boiling with aqueous alkali (*Arndt, Milde, Tschenscher*, Ber. **55**, 343), or from 1-carbethoxythiosemicarbazide, $H_5C_2OOC\cdot NH\cdot NH\cdot CS\cdot NH_2$, by treatment with NaOH (*Fromm, Nehring*, Ber. **56**, 1374); it is readily soluble in water and strongly acid. N-Arylthiourazoles are also formed from 4-arylthiosemicarbazides by heating with urea for many hours at 130°, although this reaction is not always successful [*Guha, Sen*, Quart.J.Indian Chem.Soc. **4** (1927), 43].

3,5-Dithiourazole, $NH\cdot CS\cdot NH\cdot CS\cdot NH$, (or tautomeric forms), m.p. 196°, colorless, strongly acid, readily soluble in water, prepared from trithioallophanic acid monomethyl ester, $CH_3S\cdot CS\cdot NH\cdot CS\cdot NH_2$, and hydrazine hydrate (*Arndt, Milde*, Ber. **54**, 2105). **3-Imino-5-thiourazole**, $NH\cdot CS\cdot NH\cdot C(NH)\cdot NH$, (or tautomeric forms), m.p. 303°, from hydrazothioformamide or its monomethyl ether by boiling with concentrated aqueous alkali (*loc. cit.*, p. 2099); it is a strongly acid compound, sparingly soluble in water, which is converted by methylation to the S-monomethyl ether, m.p. 135°. The latter is also formed when the S-methyl ether of hydrazothioformamide is heated, by elimination of methyl mercaptan (*loc. cit.*, p. 2097). Other compounds of this type: *Fromm*, Ann. **447**, 259.

When hydrazothioformamide is heated with acids, tetrahydro-1,3,4-thiadiazole derivatives (p. **167**) are produced (*Busch, Schmidt*, Ber. **46**, 2240; *Busch, Lotz*, J.pr. **90**, 257).

1-Phenyl-3,5-dithiourazole, m.p. 181° (*Acree, Willcox*, Ber. **37**, 184).

Diiminourazole, guanazole, $NH\cdot C(NH)\cdot NH\cdot C(NH)\cdot NH$, m.p. 206°, is obtained from α-cyanoguanidine with hydrazine (*Pellizzari*, Gazz. **24**, I, 481):



α-Cyanoguanidine Guanazole

4-Aminoguanazole, *guanazine*, m.p. 257° (dec.), from hydrazine with two molar proportions of cyanogen bromide (*Pellizzari, Repetto*, Gazz. **37**, II, 317).

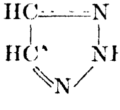
Condensed Ring Systems of 1,2,4- *and* 4,1,2-*Triazole*

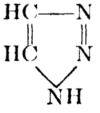
s-Triazole contains no adjacent carbon atoms, so no benzo derivatives of it exist. However, bicyclic ring systems containing the *s*-triazole ring, in which the grouping —CH═N— or —N═N— is common to the two rings, are known: *Marckwald, Rädzik*, Ber. **36**, 1111; *Näf*, Ann. **265**, 122; *Stollé*, Ber. **45**, 287.

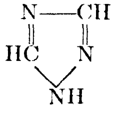
2. OXADIAZOLES

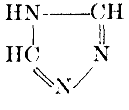
The compounds having five-membered rings containing one oxygen atom and two nitrogen atoms are called oxadiazoles or furodiazoles. The number of arrangements possible for such rings can be deduced from analogy with the triazole series, replacing the NH-member by O:

Triazole series:

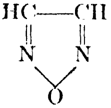

2,1,3-Triazole
(Osotriazole)

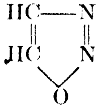

1,2,3-Triazole

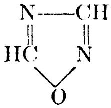

1,2,4-Triazole

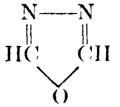

4,1,2-Triazole

Oxadiazole series:


1,2,5-Oxadiazole
Furazan

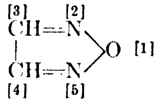

1,2,3-Oxadiazole


1,2,4-Oxadiazole
(Azoxime)

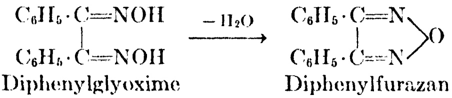

1,3,4-Oxadiazole

This analogy between the ring systems is not merely formal; it extends to their methods of preparation.

(a) Furazans, 1,2,5-Oxadiazoles:

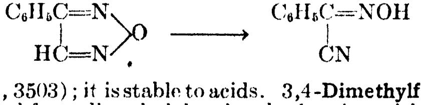


The furazans correspond to the 2,1,3-triazoles. As the latter are obtained from osazones (p. 147), so the former are prepared from glyoximes, the dioximes of *o*-diketones, with alkali:


Diphenylglyoxime Diphenylfurazan

Like the isoxazoles, the furazan derivatives in which the H-atom of both methine groups is substituted are stable compounds; if one of the methine groups is unsubstituted, rearrangement into nitriles of α-oxo carboxylic acid oximes occurs readily. The alkylfurazans can be oxidized to furazancarboxylic acids.

3-Phenylfurazan, m.p. 30°, very volatile, is formed from phenylglyoxime diacetate with soda, and is rearranged by aqueous sodium hydroxide to the oxime of benzoyl cyanide:



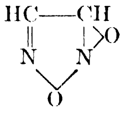
(*Russanow*, Ber. **24**, 3503); it is stable to acids. **3,4-Dimethylfurazan**, m.p. −7°, b.p. 156°, is obtained from dimethylglyoxime by heating with NH_3 at 160–170°; **3-ethyl-4-methylfurazan**, b.p. 170°, is similarly prepared from methylethylglyoxime. **3,4-Diphenylfurazan, m.p. 94°, is formed by heating azobenzoyl (*Stollé*, *Reichert*, J.pr. 123, 82); it rearranges slowly when heated into the isomeric 3,5-diphenyl-1,2,4-oxadiazole (p. 163) (*Dodge*, Ann. 264, 180). 3,4-**

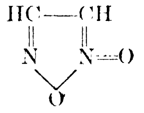
Dibenzoylfurazan, m.p. 118°, from dibenzoylfuroxan (p. 162) (*Angeli*, Ber. **26**, 529).

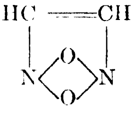
Furazan-3-carboxylic acid, m.p. 107°, is obtained by oxidation of **furazanpropionic acid**, the anhydride of dioximinovaleric acid (Vol. I). **4-Methylfurazan-3-carboxylic acid**, m.p. 74°, and **furazan-3,4-dicarboxylic acid**, m.p. 178° (dec.), are formed from dimethylfurazan with $KMnO_4$; both acids readily yield cyanoximinoacetic acid when boiled with water.

Benzo-, naphtho-, phenanthrofurazans and the like are prepared from *o*-dioximes of the benzene, naphthalene, and phenanthrene series (*cf. Zincke*, J.pr. **53**, 340; *Zincke, Schwarz*, Ann. **307**, 40).

FUROXANS are N-oxides of furazans, according to *Wieland* (*Wieland, Semper*, Ann. **358**, 36; *Wieland, Semper, Gmelin*, Ann. **367**, 52; *Wieland, Gmelin*, Ann. **367**, 80; **375**, 297); they had previously been considered glyoxime peroxides. Three structures have been suggested for them:


(I)

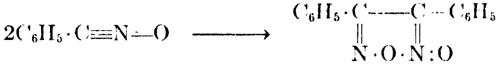

(II)


(III)

For monocyclic furoxans formula II is generally accepted (*Wieland*, Ann. **424**, 71; **444**, 7; *Kinney*, Am. **51**, 1592). Benzofuroxans (p. **162**) which undoubtedly are derived from the "bisnitroso formula" (formula III) have been prepared by *Green* and *Rowe* (J. **103**, 897; **111**, 612). According to spectroscopic data, structures II and III are equally probable, while structure I is less so (*v. Auwers*, Ber. **60**, 2122).

The most important methods for preparing furoxans are:

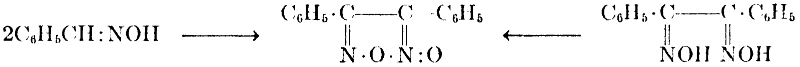
(*1*) By polymerization of nitrile oxides (Vol. III, p. 315):



$$2C_6H_5\cdot C\equiv N\rightarrow O \longrightarrow \begin{array}{c} C_6H_5\cdot C\text{——}C\cdot C_6H_5 \\ \|\qquad\| \\ N\cdot O\cdot N{:}O \end{array}$$

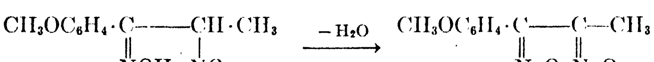
The preparation of furoxans from hydroxamic acid chlorides and nitrolic acids depends on the intermediate formation of nitrile oxides.

(*2*) By oxidation of aldoximes and glyoximes with NO_2 in ethereal solution (*Scholl*, Ber. **23**, 3496):



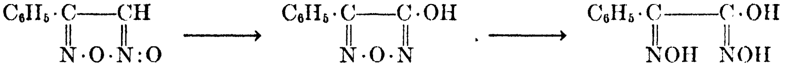
$$2C_6H_5CH{:}NOH \longrightarrow \begin{array}{c} C_6H_5\cdot C\text{——}C\cdot C_6H_5 \\ \|\qquad\| \\ N\cdot O\cdot N{:}O \end{array} \longleftarrow \begin{array}{c} C_6H_5\cdot C\text{——}C\cdot C_6H_5 \\ \|\qquad\| \\ NOH\ \ NOH \end{array}$$

(*3*) From the monomolecular pseudonitrosites (nitrites) of many propenylbenzenes by boiling with alcohol or water (*Wieland*, Ann. **329**, 238):



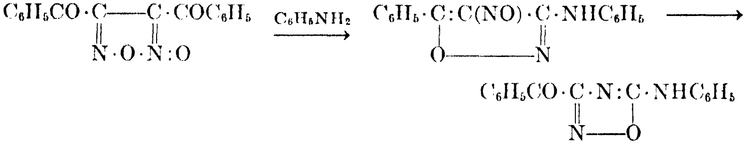
$$\begin{array}{c} CH_3OC_6H_4\cdot C\text{——}CH\cdot CH_3 \\ \|\qquad | \\ NOH\ \ NO_2 \end{array} \xrightarrow{-H_2O} \begin{array}{c} CH_3OC_6H_4\cdot C\text{——}C\text{—}CH_3 \\ \|\qquad\| \\ N\cdot O\cdot N{:}O \end{array}$$

The furoxans are reduced to the corresponding furazans by treatment with HI or Sn and hydrochloric acid or PCl_5. Like the furazans, the disubstituted furoxans are stable compounds, while the monosubstituted derivatives are easily decomposed by alkalis, forming first hydroxyfurazans, then oximes of α-oxo-hydroxamic acids:



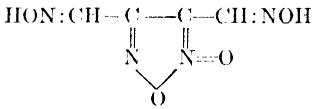
$$\begin{array}{c} C_6H_5\cdot C\text{——}CH \\ \|\qquad\| \\ N\cdot O\cdot N{:}O \end{array} \longrightarrow \begin{array}{c} C_6H_5\cdot C\text{——}C\cdot OH \\ \|\qquad\| \\ N\cdot O\cdot N \end{array} \longrightarrow \begin{array}{c} C_6H_5\cdot C\text{——}C\cdot OH \\ \|\qquad\| \\ NOH\ \ NOH \end{array}$$

Dimethylfuroxan, b.p. 222°. **Phenylfuroxan**, α-form (labile): m.p. 106-108°; β-form: m.p. 95°; from phenylglyoxime (Vol. III, p. 407) with NO_2 and from phenylacetylene by addition of N_2O_3 (*Wieland*, Ann. **424**, 71). It is converted by alkali to **phenylhydroxyfurazan**, m.p. 111° (dec.), and then split to isonitrosophenylacetohydroxamic acid (see above). When boiled with water it decomposes to form hydroxamic acid and benzonitrile oxide, which polymerizes immediately to diphenylfuroxan. The latter is also formed from benzaldoxime and benzildioxime, and by the spontaneous decomposition of benzonitrolic acid. **Dibenzoylfuroxan** results from the action of nitric acid on acetophenone. With amines, by fission and reclosing of the ring and simultaneous elimination of a benzoyl group, it gives the highly colored ***nitrosoisoxazoles*** (formerly known as *isotriazoxoles*), which rearrange when boiled with alcohol or glacial acetic acid into colorless azoximes:


$C_6H_5CO{\cdot}C$—$C{\cdot}COC_6H_5$
$N{\cdot}O{\cdot}N{:}O$
$C_6H_5NH_2$
$C_6H_5{\cdot}C{:}C(NO){\cdot}C{\cdot}NHC_6H_5$
O—N
$C_6H_5CO{\cdot}C{\cdot}N{:}C{\cdot}NHC_6H_5$
N—O

Dichloro-, dibromo- and **diiodofuroxan,** volatile, m.p. 50° and 91°, are prepared by the action of halogens on mercury fulminate (*Wieland*, Ber. **42**, 4192).

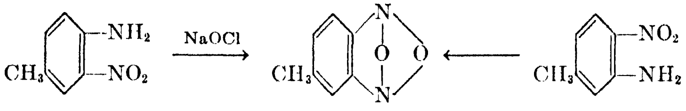
The dioxime of furoxandicarboxaldehyde



is identical with the **isocyanilic acid** discovered by *Scholvien* (J.pr. **32**, 477), which is the tetramolecular polymerization product of fulminic acid (Vol. I, p. 294). For the proof of its constitution, see *Wieland*, Ann. **444**, 7.

Furoxancarboxylic acid, m.p. 90° (dec.), slowly decomposes in water to isonitrosomalonohydroxamic acid, $COOHC(:NOH){\cdot}C(:NOH)OH$; it is formed by saponification and decarboxylation of **furoxandicarboxylic acid diethyl ester,** $(COOC_2H_5)_2C_2N_2O_2$, b.p. 164° (16 mm.), which is obtained from acetoacetic ester by treatment with fuming nitric acid with intermediate formation of isonitrosonitroacetic ester, $COORC(NO_2)(:NOH)$, and from chloroximidoacetic ester by treatment with sodium carbonate. **Furoxandicarboxylic acid amide,** m.p. 218° (dec.), is closely related to fulminuric acid, $CNCH(NO_2)CONH_2$ (Vol. I, p. 296), from which it is obtained by the action of concentrated H_2SO_4 and to which it is partially converted by boiling with water (*Wieland, Gmelin*, Ann. **367**, 80).

BENZOFUROXANS are prepared: (*1*) by oxidation of dioximes of aromatic *o*-diketones; and (*2*) by oxidation of *o*-nitroamines with hypochlorite (*Green, Rowe*, J. **103**, 897; **111**, 612). The same 5-methylbenzofuroxan (II) is obtained from *m*-nitro-*p*-toluidine (I) and from *p*-nitro-*m*-toluidine (III); this is strong evidence for the symmetrical structure of benzofuroxan.

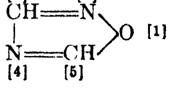


(I) (II) (III)

5-Methylbenzofuroxan, colorless needles, m.p. 97°.

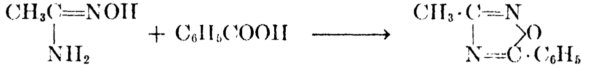
Nitroamines and nitrosoamines of the naphthalene series are converted by the same methods into naphthofuroxans and naphthofurazans (*Green, Rowe*, J. **111**, 612).

(b) 1,2,4-Oxadiazoles, Azoximes:



The 1,2,4-oxadiazoles correspond to the 1,2,4-triazoles. They are prepared:

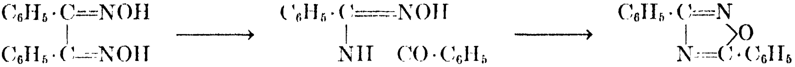
(*1*) From the oximes of acid amides and carboxylic acids, their chlorides or anhydrides (analogous to the preparation of 1,2,4-triazoles from hydrazidines):



Acetamide oxime 3-Methyl-5-phenyl-1,2,4-oxadiazole

With aliphatic aldehydes the amide oximes form dihydroöxadiazoles, which are readily oxidized to oxadiazoles; with $COCl_2$ and $CSCl_2$ they give oxadiazolones and oxadiazolethiones (*Schubart*, Ber. **19**, 1487; *Weise*, Ber. **22**, 2422; *Krümmel*, Ber. **28**, 2231).

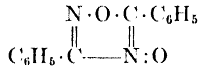
(*2*) From glyoximes or furazans (see above) by a Beckmann rearrangement (p 160) (*Angeli, Malagnini*, Gazz. **24**, II, 131):



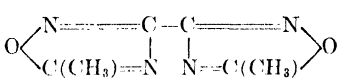
Benzil dioxime 3,5-Diphenyl-1,2,4-oxadiazole

The 1,2,4-oxadiazoles are stable, neutral compounds which are hydrolyzed with difficulty by acids or alkalis. They are very volatile with the vapors of low-boiling solvents and in the air, although they have high boiling points.

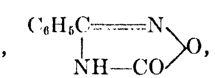
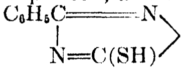
3,5-Dimethyl-1,2,4-oxadiazole, *diethenylazoxime* (*Nordmann*, Ber. **17**, 2755), is a very volatile substance. **3-Methyl-5-phenyl-1,2,4-oxadiazole**, *ethenylbenzenylazoxime*, m.p. 57°. **3,5-Diphenyl-1,2,4-oxadiazole**, *dibenzenylazoxime*, m.p. 108°, b.p. 290°, is obtained from N-benzoylbenzimide chloride with hydroxylamine (*Beckmann, Sandel*, Ann. **296**, 284), by oxidation of benzaldoxime with sodium hypochlorite and by reduction of **3,5-diphenyloxadiazole-4-oxide**,



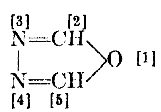
m.p. 134°, which is formed by the spontaneous decomposition of benzohydroxamic acid chloride and by action of alcoholic hydrochloric acid on tribenzonitrile oxide (*Wieland*, Ber. **42**, 806). **5,5′-Dimethyl-3,3′-bi-1,2,4-oxadiazole**,



m.p. 165° (*Zinkeisen*, Ber. 22, 2949).

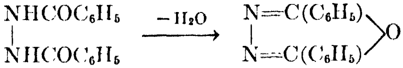
3-Phenyl-1,2,4-oxadiazol-5-one (or tautomeric form),  m.p. 198°, and **3-phenyl-1,2,4-oxadiazole-5-thiol** (or tautomeric form),  m.p. 131°, from benzamide oxime with $COCl_2$ and $CSCl_2$; the former is also obtained from phenylglyoxime with oxidizing agents, by rearrangement of the nitrile oxide, $C_6H_5C(:NOH) \cdot C:N:O$, formed as an intermediate (*Ponzio, Zanardi-Lamberti*, Gazz. **53**, 818).

(c) 1,3,4-Oxadiazoles:



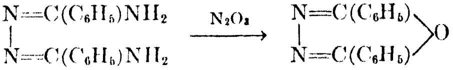
Derivatives of 1,3,4-oxadiazole, or oxybiazole, which is itself unknown, are prepared from *s*-diacylhydrazines by heating alone or with dehydrating agents;

this preparation is analogous to the formation of furans from 1,4-diketones (*cf.* pp. 15, 90; *Stollé*, Ber. **32**, 797; J.pr. **68**, 130; **69**, 506):

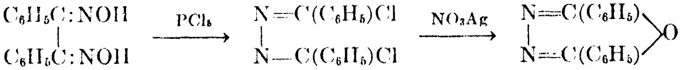


2,5-Dimethyl-1,3,4-oxadiazole, b.p. 179°, is obtained from *s*-diacetylhydrazine with acetic anhydride and from tetraacetylhydrazine by heating; it is more easily decomposed by acids and alkalis than the aromatic derivatives. **2,5-Diethyl-, dipropyl-, diisopropyl-,** and **diisobutyl-1,3,4-oxadiazole,** b.p. 198°, 227°, 209°, and 232°. **2,5-Didecyl-** and **dipentadecyl-1,3,4-oxadiazole,** m.p. 54°, b.p. 275° (22 mm.), and m.p. 72°, b.p. 215° (15 mm.) (*Stollé*, J.pr. **69**, 481 *ff.*).

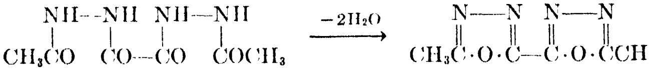
2,5-Diphenyl-1,3,4-oxadiazole, m.p. 138°, b.p. 231° (55 mm.), forms a sparingly soluble double compound with $AgNO_3$. It is prepared: (*1*) By heating dibenzoylhydrazine (see above). (*2*) From the silver salt of benzalbenzoylhydrazine and iodine (*Stollé*, J.pr. **70**, 414). (*3*) From α,α'-diaminodibenzylidenehydrazine with N_2O_3 (*Pinner*, Ann. **297**, 264):



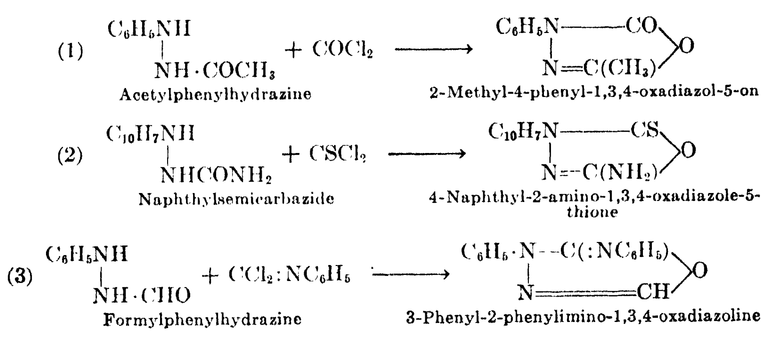
(*4*) From benzil dioxime, analogous to the formation of the isomeric 3,5-diphenyl-1,2,4-oxadiazole and diphenylfurazan (*Günther*, Ann. **252**, 60):



5,5′-Dimethyl- and **5,5′-diphenyl-2,2′-bi-1,3,4-oxadiazole,** m.p. 212° and 270°, are obtained from diacetyl- and dibenzoyloxalohydrazide by heating with P_2O_5 (*Stollé*, J.pr. **70**, 427):



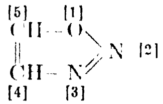
Oxo-, thio-, and **iminoöxadiazolines,** derivatives of dihydroöxadiazole, are produced from carboxylic acid and urea derivatives of phenyl- and naphthylhydrazines (Vol. III, p. 156) with phosgene, thiophosgene, and phenylisocyanic acid chloride, $CCl_2{:}NC_6H_5$ (*Freund, Kuh*, Ber. **23**, 2843; *Freund*, Ber. **24**, 4178; *Freund, König*, Ber. **26**, 2870):



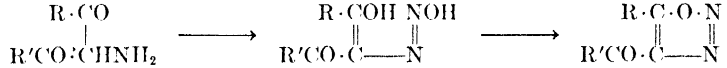
Alkoxy- and **alkylthioöxadiazolones** result from the action of $COCl_2$ on phenylcarbazic acid esters, $C_6H_5NHNH{\cdot}COOR$, and phenylthiocarbazic acid esters, $C_6H_5NHNH{\cdot}COSR$ (*Busch*, J.pr. **60**, 38).

For **dihydroöxadiazoles,** see also *Stollé*, J.pr. **68**, 417.

(d) 1,2,3-Oxadiazoles:



This ring system has been assumed to be present in the diazoanhydrides first obtained by *Wolff* (Ann. **312**, 121). These compounds are formed by the action of nitrous acid on 2-amino-1,3-dioxo compounds:

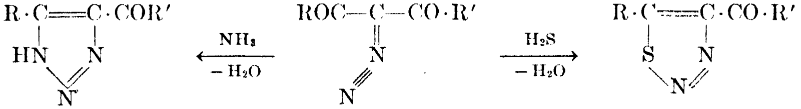


The validity of this structure has often been questioned (*Schmidlin, Massini*, Ber. **42**, 2397; *Dimroth*, Ann. **373**, 339); more recent investigations (*Staudinger* Helv. **4**, 239) demonstrate that the diazoanhydrides are better represented by the open formula of an aliphatic diazo compound:

$$(R'\cdot CO)(R\cdot CO):C{=}N{\equiv}N$$

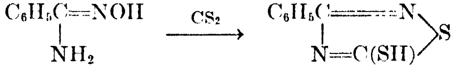
Diacyldiazomethane

The smooth conversion of these compounds to 1,2,3-triazoles with NH_3, amines, phenylhydrazine, and hydroxylamine, and to 1,2,3-thiadiazoles with H_2S (*Wolff*, Ann. **325**, 129; *Wolff, Hall*, Ber. **36**, 3612), can also be explained on the basis of the open formula:



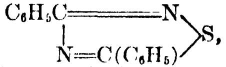
3. THIADIAZOLES

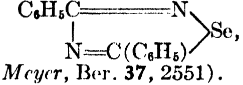
(*a*) **1,2,4-THIADIAZOLES**, *azosulfimes*, result from the reaction of amide oximes with carbon disulfide (*Crayen*, Ber. **24**, 388):

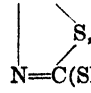


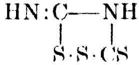
Benzamide oxime 3-Phenyl-1,2,4-thiadiazole-5-thiol

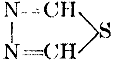
3-Phenyl-1,2,4-thiadiazole-5-thiol (or tautomeric form), m.p. 162°. With phenyl isothiocyanate, **5-anilino-1,2,4-thiadiazole** is formed.

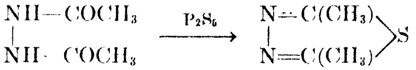
3,5-Diphenyl-1,2,4-thiadiazole (*dibenzenylazosulfime*),  m.p. 91°, is obtained by the action of iodine or persulfate on thiobenzamide (*Hofmann, Gabriel*, Ber. **25**, 1586; *v. Walther*, J.pr. **69**, 44).

3,5-Diphenyl-1,2,4-selenadiazole,  m.p. 85°, from selenobenzamide and iodine (*Becker, Meyer*, Ber. **37**, 2551).

1,2,4-Thiadiazole-3,5-dithiol (*persulfocyanic acid*) (or tautomeric form),  (*Hantzsch, Wolvekamp*, Ann. **331**, 265; *Rosenheim, Levy, Grün*-

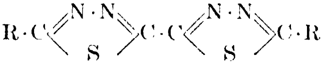
baum, Ber. **42**, 2927), is obtained in the form of its alkali salts from 5-*imino*-1,2,4-*dithiazolidine-3-thione*,  $\mathrm{HN{:}C{-}NH}$ over $\mathrm{S{\cdot}S{\cdot}CS}$ by treatment with alkalis. It is known only in its salts ($BaC_2N_2S_3 + 4H_2O$) and esters (dimethyl ester, m.p. 42°). The colorless free acid isomerizes quickly to the yellow iminodithiazolidinethione.

(*b*) 1,3,4-**THIADIAZOLES**,  are prepared analogously to the 1,3,4-oxadiazoles and 4,1,2-triazoles (pp. **163**, **154**) from *s*-diacylhydrazines by heating with P_2S_5 (*Stollé*, Ber. **32**, 797; *Seidel*, J.pr. **58**, 130):



2,5-Dimethyl-1,3,4-thiadiazole, m.p. 64°, b.p. 203°; **2,5-diphenyl-1,3,4-thiadiazole**, m.p. 142°, b.p. 259° (17 mm.), from diacetyl- and dibenzoylhydrazine. For homologues, see *Stollé*, J.pr. **69**, 158, 381, 481, etc.

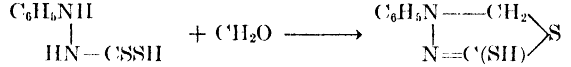
5,5′-**Dimethyl**- and 5,5′-**diphenyl-2,2′-bi-1,3,4-thiadiazole**:



m.p. 238° and 252°, from diacetyl- and dibenzoyloxalohydrazide with P_2S_5 (*Stollé*, J.pr. **70**, 429).

2,5-Dimethyl- and **2,5-diphenyl-1,3,4-selenadiazole**, m.p. 77° and 156°, from diacetyl- and dibenzoylhydrazine by heating with phosphorus pentaselenide (*Stollé*, J.pr. **69**, 509).

THIADIAZOLINES, DIHYDRO-1,3,4-THIADIAZOLES, are formed: (*1*) By the reaction of aldehydes with phenyldithiocarbazic acid (Vol. III, p. 159) or its esters (*Busch*, Ber. **28**, 2635):

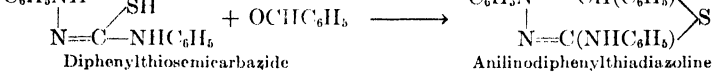


Phenyldithiocarbazic acid

3-Phenyl-5-mercapto-1,3,4-thiadiazoline, m.p. 112°

The mercaptothiadiazolines are also obtained from 1,3,4-thiadiazole-2,5-dithiol (p. 168 and *Busch*, J.pr. **60**, 28); they are strongly acid, stable to acids, and decomposed by aqueous alkali. They are readily oxidized to disulfides, which give several unusual reactions (*cf. Busch*, Ber. **29**, 2127; J.pr. **60**, 35; *Schneider*, J.pr. **67**, 246).

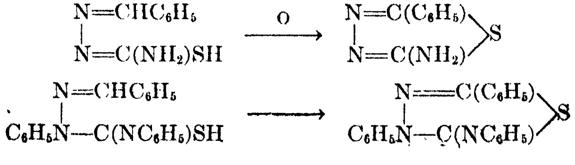
(*2*) Amino derivatives of thiadiazolines are prepared from thiosemicarbazides and aldehydes (*Busch*, *Ridder*, Ber. **30**, 849):



Diphenylthiosemicarbazide

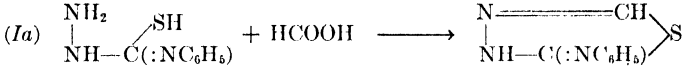
Anilinodiphenylthiadiazoline

Similarly, **2-amino-5-phenyl-1,3,4-thiadiazole** is obtained by oxidation of benzalthiosemicarbazide, and **2,4-diphenyl-5-phenylimino-1,3,4-thiadiazoline** from 1-benzal-2,4-diphenylthiosemicarbazide [*Busch*, *Holzmann*, Ber. **34**, 324; *De*, *Roy-Choudhury*, J.Indian Chem.Soc. **5**, (1928), 269], the oxidizing agent being $FeCl_3$. When H_2O_2 is used, mercaptotriazoles or their disulfides are also formed:



(*I*) Iminothiadiazolines, (*II*) oxothiadiazolines or pseudothiadiazolones, and (*III*) thiothiadiazolines are produced by the action of carboxylic acids, $COCl_2$, and CS_2 on thioformamide derivatives of hydrazine (*Busch*, Ber. **24**, 4190; **27**, 2512; J.pr. **60**, 25; Ber. **42**, 4763; *Pulvermacher*, Ber. **27**, 613; *Freund*, Ber. **29**, 2483):

(*Ia*)

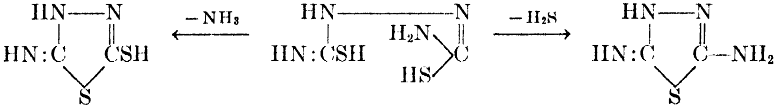


4-Phenylthiosemicarbazide

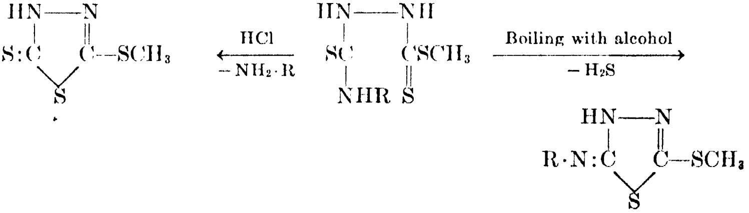
5-Phenyliminothiadiazoline, m.p. 173°

For the analogous reaction of 4-arylthiosemicarbazides with CS_2, see *Guha*, *Rây*, Am. **47**, 385.

(*Ib*) Hydrazothioformamide and its substitution products are easily converted to thiadiazolines. The reaction proceeds in two directions (*Busch*, *Lotz*, J.pr. **90**, 259):



(*Ic*) The ring closure of 4-alkylthiosemicarbazide-1-dithiocarboxylic acid esters, $R·NH·CS—NH·NH·C:SSCH_3$, also takes place in two ways, according to the reaction conditions [*Guha*, *Guha*, Quart.J.Indian Chem.Soc. **4** (1927), 161]:

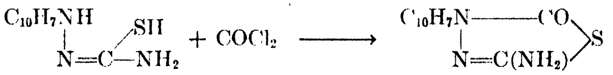


Both triazoles and thiadiazoles can be obtained from hydrazothioformamide, $H_2N·CS·NH·NH·CS·NH_2$, or its monoaryl derivatives, depending on the reaction conditions (*Arndt*, *Milde*, *Tschenscher*, Ber. **55**, 341; *Fromm*, *Soffner*, *Frey*, Ann. **434**, 285; *Fromm*, *Jokl*, Mo. **44**, 297).

5-**Iminothiadiazoline** (or **aminothiadiazole**), $S·C(NH)·NH·N:CH$, m.p. 191°, from formylthiosemicarbazide [*Freund*, *Meinecke*, Ber. **29**, 2511; for other iminothiadiazolines, see *De*, *Roy-Choudhury*, J.Indian Chem.Soc. **5** (1928), 269].

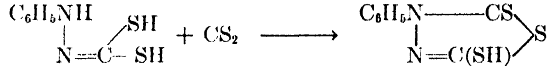
2-**Imino**-1,3,4-**thiadiazolidone**-5, $S·C(:NH)·NH·NH·CO$, m.p. 177° (formerly thought to be thiourazole), from hydrazine-1-carboxamide-2-thiocarboxamide with acids (*Arndt*, *Milde*, *Tschenscher*, Ber. **55**, 341). 5-**Imino**-1,3,4-**thiadiazoline**-2-**thiol**, $S·C(SH):N·NH·C(:NH)$, m.p. 245° (dec.) (formerly thought to be dithiourazole), from hydrazothioformamide with acids, NH_3 being eliminated (*Busch*, *Schmidt*, Ber. **46**, 2240; *Arndt*, *Milde*, Ber. **54**, 2090). 5-**Phenylimino**-1,3,4-**thiadiazoline**-2-**thiol**, m.p. 219°, from hydrazothioformanilide, with elimination of aniline. These same starting materials yield triazole derivatives in alkaline media (*Arndt*, *Milde*, *Tschenscher*, Ber. **55**, 341).

(*II*)

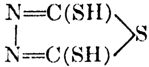


Naphthylthiosemicarbazide

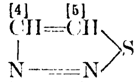
3-Naphthyl-5-amino-1,3,4-thiadiazol-2-one. m.p. 250°

(*III*) 

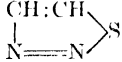
5-Mercapto-3-phenyl-1,3,4-thiadiazoline-2-thione, m.p. 91°

1,3,4-**Thiadiazole-2,5-dithiol** (or tautomeric forms), , m.p. 168° (dec.), from hydrazine and CS_2; oxidation with $KMnO_4$ converts it to thiadiazoledisulfonic acid, $N_2C_2(SO_3H)_2S$. When oxidized with iodine the mercaptothiadiazoles give disulfides: thiadiazole-S-S-thiadiazole, which react with ammonia and amines in an unusual way to give hydrosulfamines, thiadiazole-SNH_2, derivatives of thiohydroxylamine, $HS\cdot NH_2$. The arylhydrosulfamines: thiadiazole-$SNHC_6H_5$ rearrange to *p*-aminobenzenethiol ethers: $NH_2\cdot C_6H_4\cdot S$-thiadiazole. For this and other reactions of thiadiazolines, see *Busch*, J.pr. **60**, 25; *Lingenbrink*, J.pr. **61**, 330.

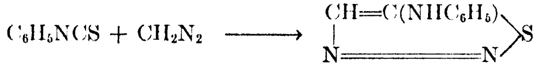
Thiadiazolidines, derivatives of tetrahydro-1,3,4-thiadiazole, have been obtained in the form of their 2,5-arylimines by oxidation of *s*- or *as*-diarylthioureas with H_2O_2 [*Chakrabarti, De*, J.Indian Chem.Soc. **5** (1929), 661].

(*c*) 1,2,3-THIADIAZOLES, , are prepared from 1,2,3-oxadiazoles (p. 165) by treatment with H_2S in the presence of alkali (*Wolff*, Ann. **333**, 1; *Wieland*, *Block*, Ber. **39**, 1491). For the formulas, see p. 165.

The 1,2,3-thiadiazoles are weakly basic compounds, stable to acids and decomposed by alkali or reducing agents with liberation of hydrogen sulfide. With $HgCl_2$ they form crystalline compounds; they also add methyl iodide.

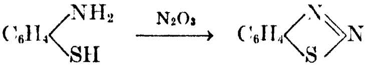
1,2,3-**Thiadiazole**, , b.p. 157°, d°1.32, 5-**methyl**- and 5-**phenyl**-1,2,3-**thiadiazole**, b.p. 184° and m.p. 53°, are obtained from their carboxylic acids. 5-**Methyl**- and 5-**phenyl**-1,2,3-**thiadiazole**-4-**carboxylic acid ester**, m.p. 35° and 42°, from diazoacetoacetic ester anhydride and diazobenzoylacetic ester anhydride (Vol. III, p. 433) with H_2S. 5-Methyl-1,2,3-thiadiazole-4-carboxylic acid is oxidized by permanganate to 1,2,3-**thiadiazole**-4,5-**dicarboxylic acid**, which is decarboxylated to 1,2,3-**thiadiazole**-4-**carboxylic acid** on fusion. 5-**Methyl**-4-**acetyl**-1,2,3-**thiadiazole**, oil, from 2,4-pentanedione diazoanhydride. 5-**Phenyl**-4-**acetyl**- and 5-**methyl**-4-**benzoyl**-1,2,3-**thiadiazole**, m.p. 70° and 43°, are both formed from 1-phenyl-1,3-butanedione diazoanhydride (*Wolff*, Ann. **325**, 169; **333**, 1).

The addition product of phenyl isothiocyanate and diazomethane is a derivative of 1,2,3-thiadiazole (*v. Pechmann*, *Nold*, Ber. **29**, 2588):

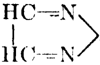


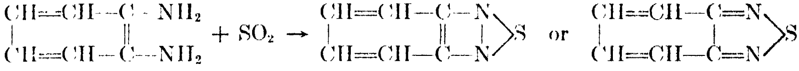
5-Anilino-1,2,3-thiadiazole, m.p. 172° (dec.)

BENZOTHIADIAZOLES, *phenylenediazosulfides*, analogous to the azimidobenzenes (Vol. III, p. 108), are formed from *o*-aminobenzenethiols with N_2O_3:



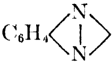
The benzothiadiazoles are much more stable than benzoöxadiazoles from *o*-aminophenols; they resemble azoimides in stability, since they lose nitrogen only at elevated temperatures, without deflagration, forming diphenylenedisulfides, $C_6H_4S_2C_6H_4$. They are weak bases and add alkyl iodides (*Jacobson*, Ann. **277**, 214). **Benzothiadiazole**, *phenylenediazosulfide*, $C_6H_4N_2S$, m.p. 35°, b.p. 129° (10 mm.); **trimethylbenzothiadiazole**, *cumylenediazosulfide*, $C_6H(CH_3)_3N_2S$ m.p. 85°.

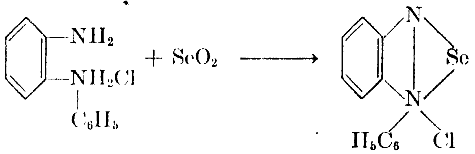
(*d*) **1,2,5-THIADIAZOLE,**  corresponds to furazan. **BENZISOTHIADIAZOLES, piazthioles,** are prepared by heating *o*-phenylenediamines with sulfurous acid (*Hinsberg*, Ber. **22**, 2895; **48**, 1613):



o-Phenylenediamine Benzisothiadiazole (piazthiole), m.p. 44°, b.p. 206°

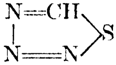
The benzisothiadiazoles are weak bases, stable to oxidizing agents; when reduced they give *o*-diamines.

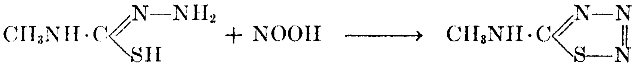
2,1,3-**BENZOSELENADIAZOLES** or **piaselenoles,** which correspond to the benzisothiadiazoles, are easily obtained from *o*-diamines with selenous acid; they are as stable as the benzisothiadiazoles. **2,1,3-Benzoselenadiazole,** *piaselenole,*  m.p. 76°, forms a perchlorate (*Battegay, Véchot*, Bull. [4] **37**, 1271). **4-Nitro-2,1,3-benzoselenadiazole,** m.p. 190° (*Fourneau, Tréfouel*, Bull. [4] **41**, 448). **Methyl-2,1,3-benzoselenadiazole,** *tolupiaselenole,* $C_7H_6(N_2Se)$, m.p. 73°, b.p. 267°. With mineral acids benzoselenadiazoles form salts (piaselenazonium salts). Addition compounds are formed directly by the action of selenium dioxide on *o*-aminodiphenylamine hydrochloride (*Battegay, Véchot*, Bull. [4] **37**, 1271):



FIVE-MEMBERED RINGS WITH FOUR HETERO ATOMS

1. THIATRIAZOLES

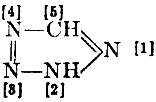
1,2,3,4-**THIATRIAZOLES** or **triazsulfoles,**  This ring is said to occur in a series of compounds formed by the action of nitrous acid on thiosemicarbazide and alkylthiosemicarbazides, although phenylthiosemicarbazide gives a tetrazole derivative (*Freund, Schwarz*, Ber. **29**, 2491; *cf. Oliveri-Mandalà*, Gazz. **44**, I, 672):



The aminothiatriazoles so obtained are decomposed by boiling water into sulfur, nitrogen, and cyanamide and by concentrated hydrochloric acid into nitrogen and *thiocyanamides.*

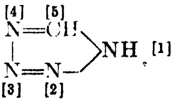
Methylamino-, ethylamino-, and **allylamino-1,2,3,4-thiatriazole,** m.p. 96°, 67°, and 54°; **amino-1,2,3,4-thiatriazole,** from thiosemicarbazide and N_2O_3, detonates at 129°.

2. TETRAZOLES



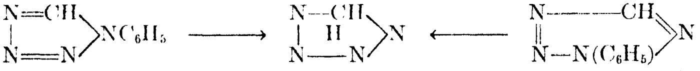
2,1,3,4-Tetrazole

and



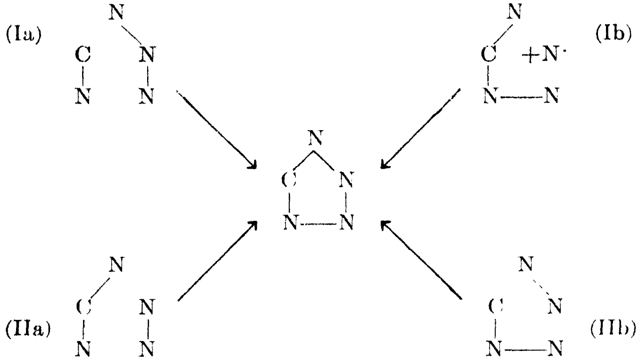
1,2,3,4-Tetrazole

On the basis of these structural formulas, the synthesis of two isomeric tetrazoles should be possible but tautomeric N-unsubstituted tetrazoles and C-alkyltetrazoles corresponding to the two forms have not been obtained. This is due to the same ambiguity in the position of the imine hydrogen which has already been observed in other azoles (pyrazoles, imidazoles, triazoles). However, a 1-phenyl-1,2,3,4-tetrazole and a 2-phenyl-2,1,3,4-tetrazole are known; when the phenyl groups are removed by oxidation, the same tetrazole is formed from both compounds:



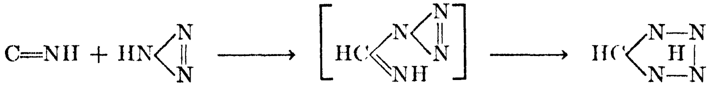
1-Phenyl-1,2,3,4-tetrazole Tetrazole 2-Phenyl-2,1,3,4-tetrazole

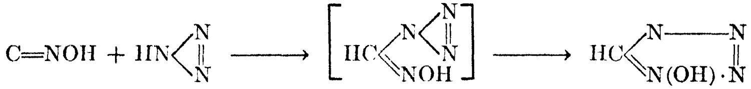
The reactions leading to the formation of the tetrazole ring can be outlined in this way:



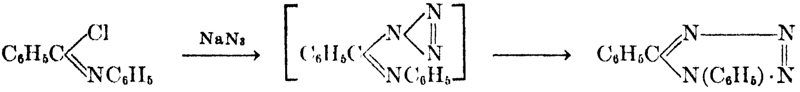
(Syntheses of type IIa have not yet been reported.)

Tetrazoles are prepared: (*1*) By condensation of hydrazoic acid with hydrocyanic acid and fulminic acid and their derivatives, isonitriles, cyanogen bromide, and cyanoformic acid ester, probably by intermediate formation of imide azides and hydroxamic acid azides [*Dimroth*, *Fester*, Ber. **43**, 2219; *Palazzo*, Atti accad. Lincei [5] **19** (1910), I, 218; *Oliveri-Mandalà*, *Alagna*, Gazz. **40**, II, 441; *Oliveri-Mandalà*, Gazz. **41**, I, 59]:

(a) 

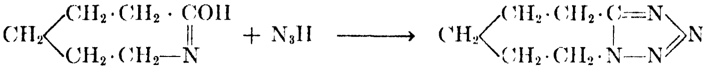
(b) 

(*2a*) From imide chlorides and similar compounds with sodium azide, also by primary formation of imidazides (*Forster*, J. **95**, 184; *Schroeter*, Ber. **42**, 3359):



In the case of guanyl azide (carbamide imide azide), $NH_2C(:NH)N_3$ (from aminoguanidine and nitrous acid), the ready conversion to aminotetrazole has been observed (*Hantzsch*, *Vogt*, Ann. **314**, 339).

(*2b*) By the action of hydrazoic acid on many acid amides and lactams or their reactive enol forms in the presence of concentrated H_2SO_4 or other acids (*cf. Schmidt*, Ber. **57**, 706; U. S. Pat. 1564631, 1925):

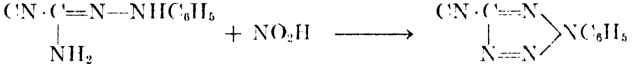


ε-Aminocaproic acid lactam

6,7,8,9-Tetrahydro-5-azepotetrazole, pentamethylenetetrazole (Cardiazole, Metrazole)

Many ketones react with two molecular proportions of hydrazoic acid to give tetrazoles, first forming acid amides which react with more N_3H according to the above equation (*Schmidt*, Ber. **57**, 706).

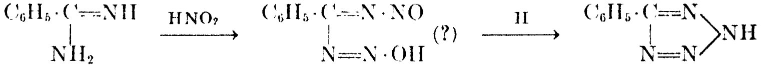
(*3*) From hydrazidines (amidrazones), such as benzhydrazidine (*Pinner*, Ber. **27**, 995; Ann. **297**, 229) and dicyanophenylhydrazine (*Bladin*, Ber. **19**, 2598), by treatment with nitrous acid, analogous to the formation of triazoles:



Dicyanophenylhydrazine

2-Phenyl-5-cyano-2,1,3,4-tetrazole

(*4*) From amidines by the action of nitrous acid, followed by reduction of the so-called dihydroxytetrazotic acids first formed (*Pinner*, Ber. **27**, 994; *Lossen, Lossen*, Ann. **263**, 101; *Lossen, Statius*, Ann. **298**, 90):

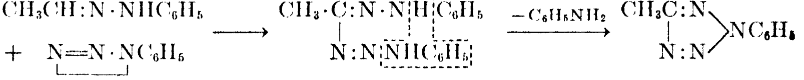


Benzamidine

Dihydroxytetrazotic acid

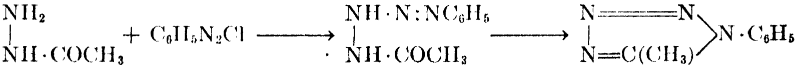
5-Phenyltetrazole

(*5*) By condensation of triazobenzene with phenylhydrazones of aldehydes by means of sodium alcoholate in alcoholic solution, aniline being eliminated (*Dimroth, Merzbacher*, Ber. **43**, 2899):



This synthesis is analogous to the preparation of 2,1,3-triazoles from osazones (p. 147).

(*6*) By the action of alkalis on the diazohydrazides formed from mono- and diacylhydrazines with diazonium salts (*Dimroth, de Montmollin*, Ber. **43**, 2904):



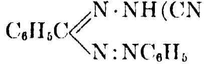
(*7*) By oxidation of suitable tetrazolium compounds, the oxidation products of formazyl compounds (Vol. III, p. 312).

Behavior.—The tetrazole ring, containing four N-atoms and one C-atom is generally more stable than the pyrrole ring and the azole rings containing less nitrogen. For example, as in the case of the pyrroles and azoles, the N-phenyl derivatives of tetrazoles can be converted to tetrazoles, by nitration to N-nitrophenyltetrazoles, reduction to N-aminophenyltetrazoles and oxidation. Unlike the slightly basic pyrrole and lower azoles, tetrazole is strongly acid, due to the influence of the N-atoms. While pyrrole is in many respects similar to phenol (p. 28), tetrazole is comparable to trinitrophenol. The silver and copper salts of tetrazole detonate violently when heated. The tetrazoles and their salts (Pb) are used in priming compositions (Ger. Pat. 370574, 1920; Brit. Pat. 201009, 1922; U. S. Pat. 1580572, 1922).

TETRAZOLE, m.p. 156°, sublimable, is obtained: (*1*) from hydrazoic acid and hydrocyanic acid (Ger. Pat. 390396, 1922; Frdl. **XIV**, 349); (*2*) by treatment of diazotized aminotetrazole with alcohol (*Thiele*, *Ingle*, Ann. **287**, 243); (*3*) by oxidation of tetrazolethiol with nitric acid; (*4*) by oxidation of 2-(4′-aminophenyl)-2,1,3,4-tetrazole-5-carboxylic acid (*Bladin*, Ber. **25**, 1412) and of 1-(4′-aminophenyl)-1,2,3,4-tetrazole (*Freund*, *Paradies*, Ber. **34**, 3120); (*5*) by oxidation of di-*p*-hydroxyphenyltetrazolium betaine (p. 174); and (*6*) by the oxidation of tetrazolo[*a*]quinoline, the so-called naphthotetrazole (*Marckwald*, *Meyer*, Ber. **33**, 1890). *Sodium salt*, $CN_4HNa + H_2O$; *barium salt*, $(CN_4H)_2Ba + 3^1/_2\ H_2O$. When heated with concentrated hydrochloric acid tetrazole decomposes into CO_2, N_2, and $2NH_3$.

5-Phenyltetrazole decomposes into diphenyltriazole (p. 155) and diphenyltetrazine (p. 324 and *Lossen*, *Statius*, Ann. 298, 96) when carefully heated to 218°; it is prepared from benzylidenedihydroxytetrazotic acid or from benzylidenehydrazidine. **5-Tolyl-**, **5-furyl-**, and **5-anisyltetrazole** are obtained from the corresponding hydrazidines or amidines (*Pinner*, *Caro*, Ber. **28**, 465; *Lossen*, *Kirschnick*, Ann. **298**, 105).

1-Methyl- and **1-ethyl-**1,2,3,4-**tetrazole**, m.p. 37° and b.p. 156° (14 mm.), from the isonitriles and hydrazoic acid. The isomeric 2-**methyl**-2,1,3,4-**tetrazole**, **m.p.** 145°, is formed by methylation of 5-cyanotetrazole (see p. 173) and removal of the cyano group. **2-Phenyl**-2,1,3,4-**tetrazole**, $C_6H_5 \cdot N \cdot N : CH \cdot N : N$, **oil,** from its carboxylic acid (*Wedekind*, Ber. **31**, 948). **1-Phenyl**-1,2,3,4-**tetrazole**, $C_6H_5 \cdot N \cdot CH : N \cdot N : N$, m.p. 66°, from phenyl isocyanide and N_3H, from diformylhydrazine and benzenediazonium chloride in alkaline solution, and from its mercaptan by oxidation with chromic acid (*Freund*, *Paradies*, Ber. **34**, 3120). 1,5-**Dimethyl**-1,2,3,4-**tetrazole**, m.p. 71°, by treatment of acetone with N_3H in the presence of concentrated sulfuric acid (U. S. Pat. 1599493, 1926). 1-**Phenyl**-5-**methyl**-1,2,3,4-**tetrazole**, $C_6H_5N \cdot C(CH_3) : N \cdot N : N$, m.p. 97.5°, from acetyl- and diacetylhydrazine according to method *6*. 2-**Phenyl**-5-**methyl**-**2,1,3,4-tetrazole,** $C_6H_5 \cdot N \cdot N : C(CH_3) \cdot N : N$, m.p. 40°, by method *5*. 1,5-**Diphenyl**-1,2,3,4-**tetrazole**, $C_6H_5N \cdot C(C_6H_5) : N \cdot N : N$, m.p. 146°, is prepared by the reaction of benzanilide imide chloride with sodium azide (Vol. III, p. 307), from benzoylhydrazine and benzenediazonium chloride by method *6* and from the reaction product of benzophenone chloride and sodium azide by a shifting of atoms similar to the Beckmann rearrangement (*Manchot*, Ber. **43**, 3359). 2,5-**Diphenyl**-2,1,3,4-**tetrazole**, $C_6H_5N \cdot N : C(C_6H_5) \cdot N : N$, m.p. 107°, is obtained from benzaldehyde phenylhydrazone and phenylazide, by oxidation of *p*-hydroxyphenyldiphenyltetrazolium hydroxide with $KMnO_4$, and by oxidation of guanazylbenzene,



$C_6H_5C\begin{cases} N \cdot NH(CN_2H_3) \\ N : NC_6H_5 \end{cases}$

(from benzalaminoguanidine and benzenediazonium chloride), with N_2O_3 or nitric acid (*Wedekind*, Ber. **30**, 449); it is a very stable compound (*Wedekind*, Ber. **29**, 1854). **Bitetrazole**, $(CHN_4)_2$, m.p. 254°, is produced by oxidation of the addition product of cyanogen and hydrazine with N_2O_3 (*Angeli*, Gazz. **23**, II, 101) or by oxidation of the reaction product of cyanotetrazole and hydrazine with HNO_2 (*Oliveri-Mandalà*, Gazz. **54**, 774; *cf. Lifschitz*, *Donath*, Rec. **37**, 270).

5-**Chlorotetrazole**, m.p. 120° (dec.); 5-**bromotetrazole** $BrCHN_4$, m.p. 156°, from cyanogen bromide and hydrazoic acid or from 5-aminotetrazole (*Stollé*, Ber. **62**, 1123).

5-**Aminotetrazole**, *aminotetrazotic acid*, $C(NH_2)N_4H + H_2O$, m.p. 199° (*Stollé*, Ber. **62**, 1120), is formed from guanidinediazonium nitrate with HNO_2, after primary formation of guanyl azide (carbamide imide azide) (Vol. I, p. 516), or from dicyandiamide with aq. hydrazoic acid (*Stollé*, *loc. cit.*). Aminotetrazole can be diazotized in acid solution like a primary aromatic amine (*Bülow*, Ber. **42**, 4436; *Stollé*, Ber. **62**, 1122); the tetrazolediazonium sulfate solution undergoes the usual conversions of aromatic diazonium compounds (5-hydroxytetrazole, 5-

bromotetrazole, *etc.*). When reduced, diazotized aminotetrazole gives 5-**hydrazinotetrazole,** $C(NHNH_2)N_4H$, m.p. 199° (dec.). The latter is converted by HNO_2 to 5-**triazotetrazole,** $C(N_3)N_4H$, a crystalline substance, extremely explosive (*Thiele, Ingle*, Ann. **287,** 238). Oxidation of 5-aminotetrazole in strongly alkaline solution with $KMnO_4$ gives salts of **azotetrazole,** $(HN_4C)N:N(CN_4H)$ (*Thiele*, Ann. **303,** 57), which is unstable in the free condition, is split by mineral acids to hydrazinotetrazole, nitrogen, and formic acid, and is reduced by Mg-powder to **hydrazotetrazole,** $(HN_4C)NH\cdot NH(CN_4H)$, a white powder which explodes when heated. When solutions of hydrazotetrazole or azotetrazole are treated with bromine, nitrogen is evolved and first 5-(dibromomethylene-hydrazino)-tetrazole (I), m.p. 177°, is formed, and later isocyanotetrabromide (II), m.p. 42° (*cf.* Vol. I and *Thiele*, Ann. **303,** 57):

$$(HN_4C)N:N(CN_4H) \longrightarrow \overset{(I)}{(HN_4C)NH\cdot N:CBr_2} \longrightarrow \overset{(II)}{Br_2C:N\cdot N:CBr_2}$$

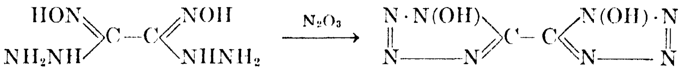
5-Aminotetrazole is transformed into 2-methyl-5-acetylamino-1,3,4-oxadiazole when boiled with acetic anhydride for a long time (*Stollé*, Ber. **62,** 1119).

2-**Phenyl**-5-**anilino**-2,1,3,4-**tetrazole,** $C_6H_5NH\cdot CN_4\cdot C_6H_5$, m.p. 163°, and its homologues are obtained from aminodiarylguanidines with N_2O_3 (*Busch, Bauer*, Ber. **33,** 1061).

1,2,3,4-**Tetrazol**-1-**ol,** from fulminic acid and N_3H (Vol. I, p. 294), decomposes at 145° with a flash. 5-**Phenyl**-1,2,3,4-**tetrazol**-1-**ol,** $HO\overline{N\cdot C(C_6H_5):N\cdot N:N}$, m.p. 121° (dec.), is prepared from benzohydroxamic acid chloride and sodium azide, and from benzoylhydrazine oxime with HNO_2, presumably after intermediate formation of the unstable benzohydroxamic acid azide.

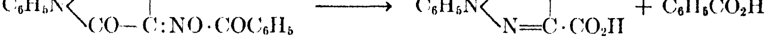
1-**Phenyl**-1,2,3,4-**tetrazol**-5-**ol** (or tautomeric form), $C_6H_5\overline{N\cdot C(OH):N\cdot N:N}$, m.p. 187°, from hydrazoformic acid esters by method *6*. 5-Alkoxytetrazoles are produced by the action of hydrazoic acid on azoformic acid esters (Vol. I, p. 504). For the course of the reaction, see *Stollé, Adam*, Ber. **57,** 1656.

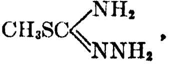
5,5′-**Bi**(1,2,3,4-**tetrazol**-1-**ol**) explodes at 176° and when rubbed vigorously; it is prepared from oxalhydrazide oxime and nitrous acid (*Wieland*, Ber. **42,** 4201):



5-**Cyanotetrazole** is obtained when gaseous dicyanogen is passed through an aqueous solution of hydrazoic acid, according to equation *Ia* (p. 170).

5-**Tetrazolecarboxylic acid ethyl ester,** $(COOC_2H_5)CN_4H$, m.p. 86°, from cyanoformic acid ester and N_3H, yields tetrazole when saponified. 2-**Phenyl**-2,1,3,4-**tetrazole**-5-**carboxylic acid,** $C_6H_5\overline{N\cdot N:C(CO_2H)\cdot N:N}$, m.p. 138°, is formed by saponification of 2-phenyl-5-cyanotetrazole (p. 171), from glyoxylic acid phenylhydrazone by method *5* and from 1-phenyl-4-(benzoylisonitroso)-1,2,3-triazol-5-one (p. 150) by rearrangement in cold aqueous sodium hydroxide solution (*Dimroth, Dienstbach*, Ber. **41,** 4055):

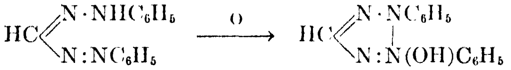


5-**Tetrazolethiol** (or tautomeric form), m.p. 205° (dec.), is obtained from its methyl ether, $CH_3S\cdot CN_4H$, m.p. 151° (dec.), by heating with hydriodic acid. The ether is prepared from methylthiosemicarbazide,  $CH_3SC{<}^{NH_2}_{NNH_2}$, with

N_2O_3. The mercaptan is oxidized by nitric acid to tetrazole and by $KMnO_4$ to **tetrazolesulfonic acid**, $C(SO_3H)N_4H$, which is converted by alkali fusion to **5-tetrazolol** (*or tautomeric form*), $C(OH)N_4H$, m.p. 254° (*Freund, Paradies*, Ber. **34**, 3110).

1-Phenyl-5-tetrazolethiol (or tautomeric form), $HS\cdot\overline{C:N\cdot N:N\cdot N}\cdot C_6H_5$, m.p. 147–150° (dec.), from thiocarbanilyl azide by boiling with sodium carbonate solution (*Freund, Hempel*, Ber. **28**, 78; *Oliveri-Mandalà*, Gazz. **44**, I, 670). Oxidation with $KMnO_4$ gives **1-phenyltetrazolesulfonic acid**, $C(SO_3H)N_4C_6H_5$, from which the sulfo group is split by heating with HCl, leaving 1-phenyl-1,2,3,4-tetrazol-5-ol (p. 173).

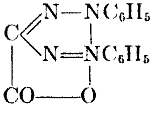
TETRAZOLIUM COMPOUNDS are obtained by the oxidation of the usually highly colored formazyl derivatives, as the *v*-tetrazines are prepared from osazones (p. 323):

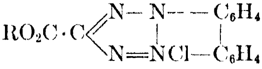

Formazyl hydride Diphenyltetrazolium hydroxide

For the effect of substituents on this ring-closure, see *Wedekind, Stauwe*, Ber **31**, 1746. The oxidation is best accomplished with amyl nitrite and hydrochloric acid, which gives the salts; the free tetrazolium compounds result from the oxidation with mercuric oxide in alcohol. Like all ammonium hydroxides, the tetrazolium hydroxides are strong bases. When reduced with ammonium sulfide, they are converted back to formazyl compounds.

Diphenyltetrazolium chloride, $CHN_4(C_6H_5)_2Cl$, m.p. 268° (dec.), is formed by the decarboxylation of **diphenylcarboxytetrazolium chloride**, $CN_4(C_6H_5)_2Cl\cdot COOH$, m.p. 257° (dec.); the ester of this acid is prepared from formazylcarboxylic acid ester and, like the acid itself, is easily converted to a betaine (I). **(Dihydroxydiphenyl)-tetrazolium betaine**, m.p. 179° (dec.), obtained by the same method, can be oxidized to tetrazole (*v. Pechmann, Wedekind*, Ber. **28**, 1693), which is evidence of the relation between the tetrazoles and the tetrazolium compounds. Similarly, **(*p*-hydroxyphenyl)-diphenyltetrazolium chloride** gives diphenyltetrazole (*Wedekind*, Ber. **29**, 1852). **Carbethoxybiphenylenetetrazolium chloride** (?) (II), from cycloformazylcarboxylic acid ester (?) (*Wedekind*, Ann. **295**, 335):

(I)





(II)

The physiologically important **pentamethylenetetrazole**, 6,7,8,9-*tetrahydro*-5-*azepotetrazole*, **metrazole, cardiazole**, m.p. 58° (formula: p. 171), is produced by the action of excess hydrazoic acid on cyclohexanone (*Schmidt*, Ber. **57**, 704; U. S. Pat. 1599493, 1926). It is used as a substitute for camphor. For its action on the central nervous system, see *Hildebrandt*, Arch.exptl.Path.Pharm. **116** (1926), 100.

Other condensed bicyclic derivatives of tetrazole are obtained from α-hydrazinopyridine, and tetracyclic derivatives from 2,7-dihydrazino-1,8-naphthyridine with nitrous acid (*Seide*, Ber. **59**, 2465).

Pentazoles

Attempts to synthesize the pentazole ring have not been successful (*cf. Curtius*, Ber. **48**, 1614).

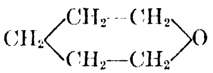
A derivative of the corresponding pentarsenole has been prepared: *pentamethylpentarsenolane* (*Auger*, C.r. **138**, 1705).

D. SIX-MEMBERED HETEROCYCLIC COMPOUNDS

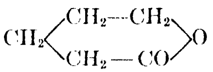
I. SIX-MEMBERED RINGS WITH ONE HETERO ATOM

1. SIX-MEMBERED RINGS WITH ONE O-ATOM

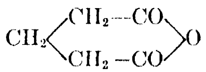
A number of compounds which belong in this class have been described in Volume I together with the aliphatic compounds to which they are related. Such compounds include the anhydrides of 1,5-glycols, the δ-lactones, such as δ-valerolactone, and the anhydrides of glutaric acids, for example:



Tetrahydropyran



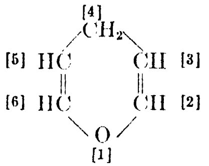
δ-Valerolactone



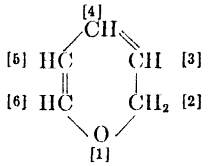
Glutaric anhydride

(a) Pyrans and Pyrones

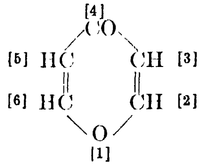
The compounds to be treated in this volume are characterized by having rings containing two double bonds:



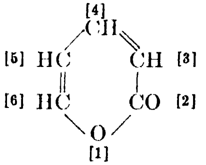
1,4-Pyran



1,2-Pyran



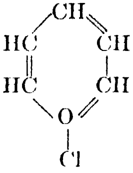
1,4-Pyrone



1,2-Pyrone

These compounds also contain a CH_2- or a CO-group, which is the reason that they resemble unsaturated aliphatic compounds in behavior; none has an aromatic character.

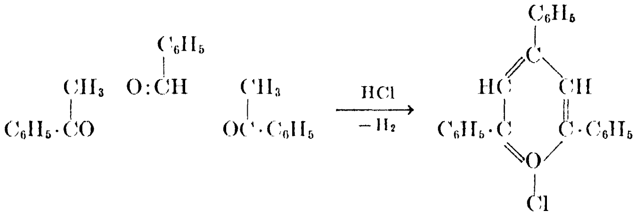
One of the striking properties of the pyran and pyrone ring system is the ease with which salts are formed with mineral acids; it is the oxygen in the ring which causes the basicity. Such oxonium salts have been prepared in large numbers from 1,4-pyrans; they are called pyrylium compounds (or pyroxonium compounds):



Pyrylium chloride

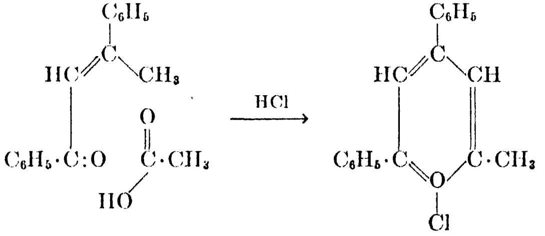
A general ring-synthetic method for the preparation of pyrylium compounds is known only for the aryl derivatives. They are obtained:

(*1*) From aromatic methyl ketones and benzaldehyde by the condensing and oxidizing action of concentrated H_2SO_4 (*Dilthey, Last*, J.pr. **94,** 50; *Dilthey*, J.pr. **95,** 107) or of acetic anhydride and sublimed ferric chloride (*Dilthey, Burger*, Ber. **54,** 825; *Schneider, Ross*, Ber. **55,** 2775):



2,4,6-Triphenylpyrylium chloride

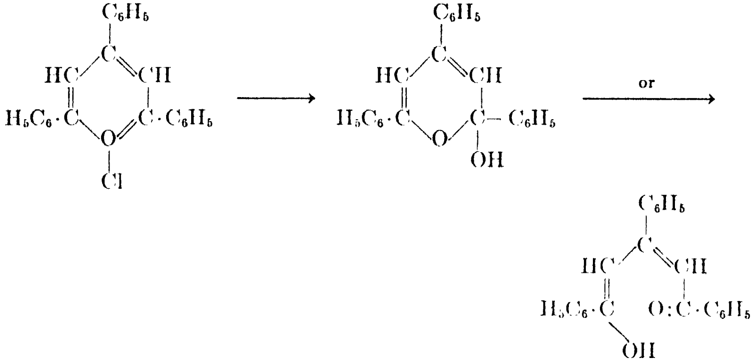
(*2*) From acetophenone and acetic anhydride (containing sulfoacetic acid). In this reaction acetophenone participates as dypnone (Vol. III, p. 578) (*Schneider, Ross*, Ber. **55,** 2776):



2-Methyl-4,6-diphenylpyrylium chloride

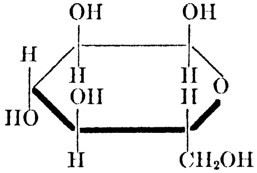
The same type of ring-closure occurs in the formation of 2-methyl-4,6-di-*m*-tolylpyrylium perchlorate from 2 mols toluene, acetic anhydride and 70% perchloric acid; first *m*-methylacetophenone is formed, and 2 mols of this react with another mol of acetic acid (anhydride) according to the above equation (*Diels, Alder*, Ber. **60,** 716).

The pyrylium compounds so prepared are usually isolated as the $FeCl_3$ double salts or as the perchlorates; they also form picrates. Pyrylium compounds substituted only by phenyl groups are converted by sodium acetate into colorless pseudo bases, pyranols, such as 2,4,6-*triphenyl-2-pyranol,* m.p. 119° (*cf. Dilthey,* J.pr. **101,** 177):



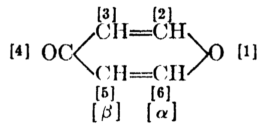
2-Methyl derivatives, on the other hand, give blue-violet products having a structure similar to quinhydrone, the pyranhydrones (*Schneider, Ross,* Ber. **55,** 2777). Compounds having hydroxyl groups on the benzene rings form violones (*Dilthey, Burger,* Ber. **54,** 825).

Many hexoses may be considered as pentahydroxytetrahydropyrans. According to a proposed system of nomenclature (*Goodyear, Haworth,* J. **1927,** 3136), these hexoses, with 1,5-oxide links, are known as pyranoses, to distinguish them from furanoses. This relationship with pyran is emphasized by the manner of writing the hexose formulas proposed by *Haworth* (Helv. **11,** 534), which is illustrated here for α-glucose (see also Vol. I, p. 690):

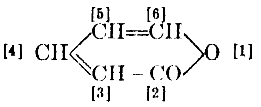


α-Glucose

Replacement of the CH_2-group by the CO-group in the corresponding pyrans gives 1,4- and 1,2-pyrone.



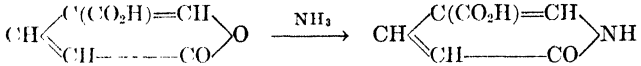
1,4-Pyrone



1,2-Pyrone

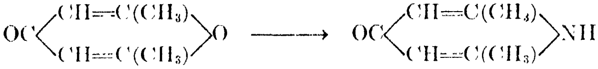
The latter may also be considered as the lactone of a δ-hydroxydiolefincarboxylic acid.

The pyrones are readily split by hydrolysis. When warmed with ammonia they are converted to pyridones (hydroxypyridines) (p. 208):



1,2-Pyrone-5-carboxylic acid, Coumalic acid

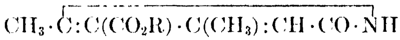
Hydroxynicotinic acid



2,6-Dimethyl-1,4-pyrone

Lutidone, 2,6-dimethyl-4(1)-pyridone

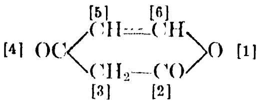
(*a*) The 1,2-pyrones are also known as coumalins. **1,2-Pyrone,** *coumalin,* and **4,6-dimethyl-1,2-pyrone,** *dimethylcoumalin,* are formed from their carboxylic acids: **coumalic acid,** *2-oxo-1,2-pyran-5-carboxylic acid* (ethyl ester, m.p. 34°), from malic acid with H_2SO_4, and **dimethylcoumalic acid,** *isodehydroacetic acid, 4,6-dimethyl-2-oxo-1,2-pyran-5-carboxylic acid,* m.p. 155°, which is obtained from acetoacetic ester with H_2SO_4 or from the sodium derivative of acetoacetic ester and β-chlorocrotonic acid ester; methyl ester, m.p. 67°, b.p. 167° (14 mm.); ethyl ester m.p. 25°, b.p. 166° (12 mm.). When the esters are treated with ammonia, an addition compound containing 2 mols of NH_3 is formed first; at higher temperatures the nitrogen enters the ring (see above), forming 3-carbethoxy-2,4-dimethyl-6(1)-pyridone:



$$CH_3\cdot C{:}C(CO_2R)\cdot C(CH_3){:}CH\cdot CO\cdot NH$$

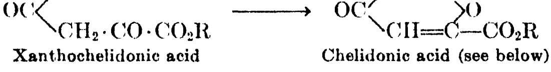
(*Anschütz, Bendix, Kerp,* Ann. **259,** 172; *Pauly,* Ber. **30,** 483). **6-Phenyl-1,2-pyrone, phenylcoumalin,** m.p. 68°, occurs in Coto bark; when reduced it forms δ-phenylvaleric acid, and when treated with ammonium acetate it gives 6-phenyl-2(1)-pyridone (*Leben,* Ber. **29,** 1673; *Ciamician, Silber,* Ber. **29,** 2659). **1,2-Pyrone-6-carboxylic acid,** m.p. 228°, is prepared from oxalocrotonic acid with alkalis [*Lapworth,* Proc.Chem.Soc. **16** (1900), 132]. **3-Phenyl-1,2-pyrone-6-carboxylic acid ester,** from 3-phenyl-2-propynylidenemalonic ester (*Claisen,* Ber. **36,** 3671). A series of 1,2-pyrone derivatives are obtained by condensation of acetylenecarboxylic acid esters with β-diketones or β-ketonic acid esters and sodium ethylate (*Ruhemann, Cunnington,* J. **75,** 778). **6-Methyl-1,2-pyrone-3,5-dicarboxylic acid ester,** m.p. 80°, by condensation of ethoxymethylenemalonic ester with sodium acetoacetic ester (*Simonsen,* J. **93,** 1022).

The following compounds are derivatives of 1,2-pyran-2,4(3)-dione:



Dehydroacetic acid, *3-acetyl-6-methyl-1,2-pyran-2,4(3)-dione* (*Benary,* Ber. **43,** 1070), prepared by boiling acetoacetic ester, by polymerization of ketene $CH_2{=}CO$ (*Staudinger, Klever,* Ber. **41,** 597), by the reaction of acetyl chloride with tertiary bases (*Wedekind,* Ann. **323,** 247) and by the action of P_2O_5 on boiling acetic anhydride (*Diels, Meyerheim,* Ber. **40,** 362). It is also formed by decarboxylation of **3-acetyl-6-methyl-2,4(3)-dioxo-1,2-pyran-5-carboxylic acid,** *dehydroacetocarboxylic acid,* which is obtained from β-oxo glutaric acid with acetic anhydride (*v. Pechmann, Neger,* Ann. **273,** 186). When heated with concentrated H_2SO_4 dehydroacetic acid is converted into **3-methyl-1,2-pyran-2,4(3)-dione,** *triacetic acid,* which regenerates dehydroacetic acid when heated with acetic anhydride and sodium acetate (*Dieckmann, Breest,* Ber. **37,** 3387). Other pyran-2,4-diones have been produced by the action of tertiary bases on monoalkylacetyl chlorides (*Wedekind,* Ann. **378,** 261).

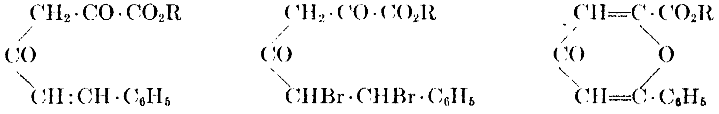
(*b*) 1,4-Pyrones are usually prepared by elimination of water from 1,3,5-triketones (*Claisen,* Ber. **24,** 111):



Xanthochelidonic acid

Chelidonic acid (see below)

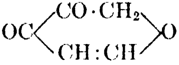
By a similar reaction benzylideneacetylpyruvic acid (I) is transformed through the dibromide (II) into a derivative of 1,4-pyrone (III) (*Borsche, Peter*, Ann. **453**, 148):



(I) (II) (III)

The 1,4-pyrones are readily converted to triketones by alkalis. Although the pyrones contain a ketone oxygen atom they do not react with hydroxylamine and the like. They do not add halogens. A characteristic reaction is the formation of salt-like addition products from pyrones, especially dimethylpyrone, and acids or metal halides. These products readily dissociate into the original components. This property is evidence of the existence of a tetravalent oxygen atom in these compounds (*Decker, v. Fellenberg*, Ann. **364**, 1; *Gomberg, Cove*, Ann. **376**, 217).

1,4-**Pyrone**, *pyrocomane*, m.p. 32°, b.p. 315°, is obtained from its carboxylic acids, comanic acid and chelidonic acid, which lose CO_2 when heated (*Willstätter, Pummerer*, Ber. **37**, 3744). 1,4-Pyrone, which may be regarded as the anhydride of *bis*(hydroxymethylene)-acetone, CH(OH):CH·CO·CH:CH(OH), can be easily decomposed into derivatives of this ketone; with aqueous sodium hydroxide and benzoyl chloride it gives the O,O′-dibenzoyl derivative, with potassium methylate, the K-salt of the monomethyl ether, $CH_3OCH:CHCOCH:$-CHOK, and by acetylation with orthoformic acid ester and hydrochloric acid, the hexaethylacetal of β-oxo glutaraldehyde, $(C_2H_5O)_2CH\cdot CH_2\cdot C(OC_2H_5)_2CH_2\cdot$-$CH(OC_2H_5)_2$ (*cf.* the fission of furan to the tetramethylacetal of succinaldehyde, p. 16). Pyrone can be readily regenerated from the derivatives of *bis*(hydroxymethylene)-acetone (*Willstätter, Pummerer*, Ber. **38**, 1161). **Mono-** and **dibromopyrone,** m.p. 114° and 157°, are produced by the action of undiluted bromine on pyrone (*Feist, Baum*, Ber. **38**, 3562). 2,6-**Dimethyl**-1,4-**pyrone,** m.p. 132° (sublimes even at 80°), b.p. 248°, is formed when dehydroacetic acid is heated with HI or, better, with hydrochloric acid (preparation: *Willstätter, Pummerer*, Ber. **38**, 1465), and also from its dicarboxylic acid (see below) (*Feist*, Ann. **257**, 253). Hydrochloride $C_7H_8O_2\cdot HCl + 2H_2O$, m.p. 85°, anhydrous, m.p. 154°; chloroplatinate, $(C_7H_8O_2)_2H_2PtCl_6$; oxalate, $(C_7H_8O_2)C_2O_4H_2$. When boiled with barium hydroxide it yields diacetylacetone, which can be converted directly back to dimethylpyrone. With methyl iodide it gives dimethyldiacetylacetone, which condenses to **tetramethyl-1,4-pyrone,** m.p. 92°, when warmed with hydrochloric acid [*Collie, Steele*, Proc.Chem.Soc. **16** (1900), 146]. When heated with ammonia dimethylpyrone forms lutidone (p. 178). **2-Phenyl-6-methyl-1,4-pyrone,** m.p. 88°, and **2,6-diphenyl-1,4-pyrone,** m.p. 139°, are obtained by condensation of phenylpropiolic acid ester with acetone and acetophenone (*Ruhemann*, J. **93**, 431).

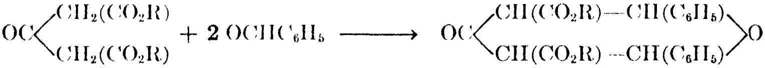
3-**Hydroxy**-1,4-**pyrone**, *pyrocomenic* or *pyromeconic acid*, m.p. 121°, b.p. 228°, is prepared by distillation of its carboxylic acids, comenic and meconic acids. With bases it forms unstable salts. With N_2O_3 it gives an isonitroso compound derived from the tautomeric *keto*-form, ; this isonitroso derivative can be transformed to 2,3,4-*trihydroxypyridine*, *pyromecazonic acid* [*Peratoner*, Atti accad.Lincei [5] **11** (1902), I, 327]. **2-Methyl-3-hydroxy-1,4-pyrone,** *maltol*, m.p. 159°, has been found in the needles of pine trees and in the bark of larches, and is formed in the roasting of malt [*Peratoner, Tamburello*, Ber. **36**, 3407; Giorn.sci.nat.econ. **25** (1905), 272].

1,4-**Pyrone-2-carboxylic acid,** *comanic acid*, m.p. 250° (dec.), results from the decarboxylation of chelidonic acid; it decomposes when boiled with lime into acetone, formic acid, and oxalic acid, and reacts with ammonia to form hydroxypicolinic acid (p. **217**). 1,4-**Pyrone**-2,6-**dicarboxylic acid, chelidonic acid, m.p.** 220°, occurs together with malic acid in celandine, *Chelidonium maius* (*Lerch*, Ann. **57**, 274), and can be easily prepared by elimination of water from xanthochelidonic acid. It forms colorless salts. When warmed with alkalis it is converted into salts of xanthochelidonic acid, which are yellow. Reduction yields γ-oxopimelic acid, *hydrochelidonic acid* (Vol. I, p. 625) and *n*-pimelic acid. Ammonia gives hydroxypyridinedicarboxylic acid (p. 217).

5-Hydroxypyrone-2-carboxylic acid, *comenic acid* [*Peratoner, Palazzo,* Giorn. sci.nat.econ. **25** (1905), 45], from meconic acid, reacts with ammonia to form dihydroxypicolinic or comenamic acid (p. **217**), which can also be obtained from **3-hydroxypyrone-2,6-dicarboxylic acid,** *meconic acid,* $C_5H(OH)(COOH)_2O_2 + 3H_2O$, which occurs in opium, bound to morphine (*How,* Ann. **83**, 352). It loses CO_2 readily; ferric oxide colors it dark red. The constitution of this acid has been determined from its decomposition products with barium hydroxide (*Peratoner, Leonardi,* Gazz. **30**, I, 539).

2,6-Dimethylpyrone-3,5-dicarboxylic acid; its ethyl ester, m.p. 80°, is prepared by elimination of water from α,γ-diacetyl-β-oxo glutaric acid ester, $CO[CH(COOR)COCH_3]_2$ (*Conrad, Guthzeit,* Ber. **20**, 154; *Peratoner, Strazzeri,* Gazz. **21**, 292).

Tetrahydropyrone derivatives result from the condensation of β-oxoglutaric acid esters with aldehydes in the presence of hydrochloric acid (*Petrenko-Kritschenko, Stanischewsky,* Ber. **29**, 994; *Petrenko-Kritschenko, Arzibascheff,* Ber. **29**, 2051):

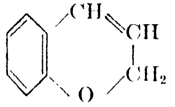


$$OC\begin{cases}CH_2(CO_2R)\\CH_2(CO_2R)\end{cases} + 2\,OCHC_6H_5 \longrightarrow OC\begin{cases}CH(CO_2R)-CH(C_6H_5)\\CH(CO_2R)-CH(C_6H_5)\end{cases}O$$

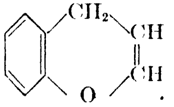
2,6-Dimethyl- and **2,6-diphenyltetrahydropyrone-3,5-dicarboxylic acid diethyl ester,** m.p. 102° and 115°; the free acids can be decarboxylated to tetrahydropyrones, which are easily converted by mineral acids to diolefin ketones. **2,6-Diphenyltetrahydropyrone,** m.p. 131°, gives dibenz lacetone. Unlike the pyrones the tetrahydropyrones yield oximes immediately (*Petrenko-Kritschenko, Plotnikoff,* Ber. **30**, 2801; *Petrenko-Kritschenko,* Ber. **31**, 1508; **32**, 809; *Petrenko-Kritschenko, Rosenzweig,* Ber. **32**, 1744). **2,6-Diphenyl-3,5-dimethyltetrahydropyrone,** $C_5H_4O_2(CH_3)_2(C_6H_5)_2$, m.p. 106°, b.p. 236° (20 mm.), is formed from diethyl ketone with 2 molar proportions of benzaldehyde in the presence of alcoholic alkali (*Vorländer, Hobohm,* Ber. **29**, 1352).

(b) Benzopyrans and Benzopyrones

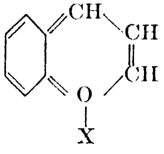
The benzopyrans are derived from the monocyclic pyrans, and the benzopyrylium compounds, from the pyrylium compounds:



1,2-Benzopyran

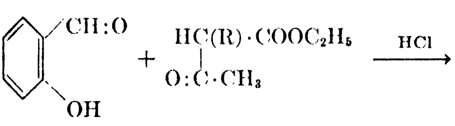


1,4-Benzopyran

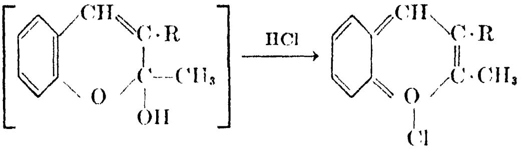


Benzopyrylium compound

(*1*) For the preparation of benzopyrylium compounds, which are the most important members of this group, gaseous hydrogen chloride is allowed to act on the ether solution of aromatic *o*-hydroxyaldehydes and α-substituted β-oxo carboxylic acid esters, 1,3-diketones (*Chatterji, Ghosh,* J. **113**, 444) or ketones of the type of methyl ethyl ketone [*Decker, v. Fellenberg,* Ann. **364**, 21; *De,* Quart.J. Indian Chem.Soc. **4** (1927), 23, 137]:



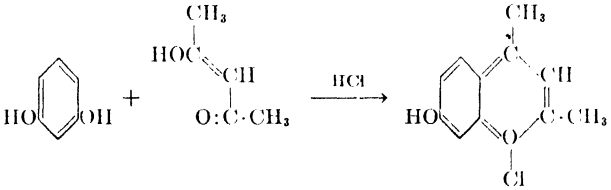
Salicylaldehyde **Subst. acetoacetic ester**



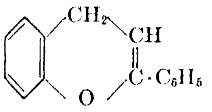
Pseudo-base,
Subst. benzopyranol

Subst. benzopyrylium
chloride

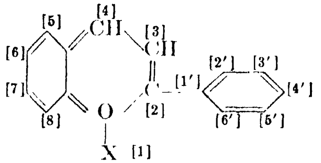
(*2*) *Bz*-Hydroxybenzopyrylium salts are formed from polyhydric phenols with hydroxyl groups in the 1,3-position and aliphatic 1,3-diketones under the influence of hydrogen chloride:



2-*Phenylbenzopyran*, which is also called flavene, and the 2-phenylbenzopyrylium or flavylium compounds are of especial significance:



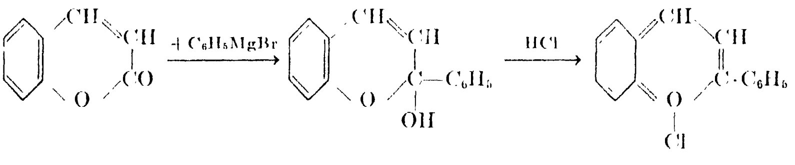
Flavene



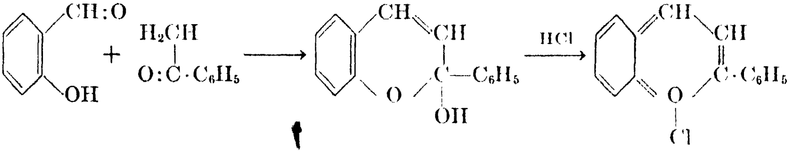
Flavylium compounds

Flower pigments are hydroxyl derivatives of this trinuclear ring system.

Synthesis of Flavylium Compounds.—(*1*) The first method of general applicability was found by *Decker* and *v. Fellenberg* (Ann. **356,** 281; **364,** 1) in the action of *phenylmagnesium bromide* on *coumarin* or substituted *coumarins:*



(*2*) The second method is derived from the ring-synthesis given (p. 180) for benzopyran. It consists in the treatment of ether solutions of acetophenone and aromatic *o*-hydroxyaldehydes with gaseous hydrogen chloride (*Decker, v. Fellenberg,* Ann. **356,** 295; **364,** 1; *Robertson, Robinson,* J. **1926,** 1951; *Irvine, Robinson,* J. **1927,** 2086):



Subst. benzopyranol (pseudo-base)

(*3*) Flavylium compounds can also be obtained by the second general method given on p. 181 for the synthesis of benzopyrylium compounds, if benzoylacetone or derivatives of it are used in place of purely aliphatic 1,3-diketones as the second component (*Bülow, Schmid*, Ber. **39**, 214, 2027).

The flavylium salts form characteristic double salts with a series of heavy-metal salts, such as $FeCl_3$, $AuCl_3$, $HgCl_2$, $CdCl_2$, sparingly soluble Pb-salts and picrates (*Karrer, Widmer*, Helv. **10**, 9, 73), which can be used for their isolation and identification. When treated with alkali they are readily converted to pyranols (see above).

Benzopyrylium chloride, $FeCl_3$ double salt, m.p. 199°. **2-Methylbenzopyrylium chloride**, $FeCl_3$ double salt, m.p. 118°. **2-Phenylbenzopyrylium chloride**, *flavylium chloride*, m.p. 70°, $FeCl_3$ double salt, m.p. 129° (*Decker, v. Fellenberg*, Ann. **356**, 298). **2,3-Diphenylbenzopyrylium chloride**, $FeCl_3$ double salt, m.p. 124°. For further benzopyrylium and naphthopyrylium compounds, see *Decker, v. Fellenberg*, Ann. **364**, 17 *ff*.

3′,4′-Dihydroxyflavylium chloride (*Robertson, Robinson*, J. **1926**, 1951); **butinidin chloride**, *7,3′,4′-trihydroxyflavylium chloride;* **apigenidin chloride**, *5,7,4′-trihydroxyflavylium chloride;* **luteolidin chloride**, *5,7,3′,4′-tetrahydroxyflavylium chloride* (*Robertson, Robinson*, J. **1926**, 1951; *Irvine, Robinson*, J. **1927**, 2086).

For derivatives of *3-phenylbenzopyran*, see *Baker, Robinson*, J. **127**, 1981; J. **1926**, 2713.

The well-known **flower pigments** of the rose, of the cornflower, of the pelargonium, and of the larkspur, as well as the pigments of the whortleberry and the grape, and many others, are hydroxyl derivatives (or, in some cases, methoxy derivatives) of a 3-hydroxyflavene (formula, p. 181). The clarification of the constitution of these substances is due to the pioneer work of *R. Willstätter* (Ann. **408**, 1–162; summary: Ber. **47**, 2865) and the more recent work of *P. Karrer* (*Karrer, Widmer*, Helv. **10**, 5, 67; **11**, 837; **12**, 292; *Karrer, et al.*, Helv. **10**, 729, 750; *Karrer, Schwarz*, Helv. **11**, 916).

The pigments occur in the flowers as glucosides, sometimes esterified with tannic acid. The glucosides are called **anthocyans**. These are split by 20% hydrochloric acid into carbohydrates and the sugar-free components, the **anthocyanidins**, which are obtained as oxonium salts. They were the starting point for the analytical work. Clues to the constitution of these pigments were obtained first from alkali fusion, and later by heating with 10–15% NaOH or 10% $Ba(OH)_2$ solution (*Karrer, Widmer*, Helv. **10**, 5) or hydrogen peroxide, and permethylation and subsequent selective hydrolysis (*Karrer et al.*, Helv. **10**, 729). Ozonide fission: *Karrer, Schwarz*, Helv. **11**, 916. One of the products of the alkali fission was phloroglucinol, and another was a hydroxy- or polyhydroxybenzoic acid such as *p*-hydroxybenzoic acid, protocatechuic acid, vanillic acid, gallic acid syringic acid (4-hydroxy-3,5-dimethoxybenzoic acid). In the anthocyans the hexose or disaccharide residue is attached to the hydroxyl group in the 3-position of the pyrylium ring, and the tannic acid radical is substituted on the aromatic nucleus condensed to this ring (*Karrer et al.*, Helv. **10**, 730).

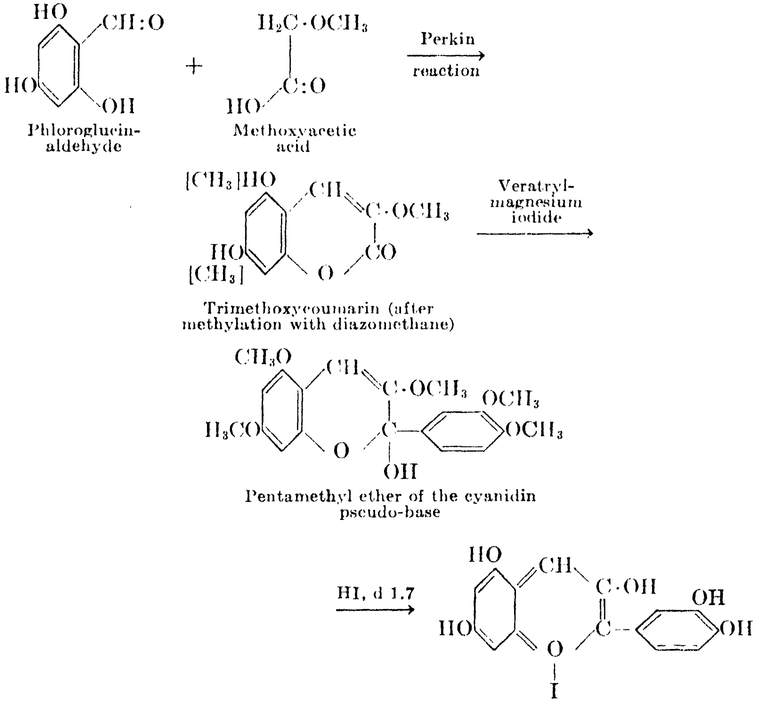
THE MOST IMPORTANT ANTHOCYANIDIN CHLORIDES. (For the formula and numbering of the flavylium compounds, see p. 181.) **Pelargonidin chloride**, *3,5,7,4′-tetrahydroxyflavylium chloride*, m.p. over 350°, from the pelargonium, aster, and dahlia (*Willstätter*, Ann. 408, 54), balm (*Karrer, Widmer*, Helv. **10**, 67; **11**, 837), and pomegranate blossoms (*Karrer, Widmer*, Helv. **10**, 76). **Cyanidin chloride**, *3,5,7,3′,4′-pentahydroxyflavylium chloride*, m.p. 220°, from the rose, cornflower, and cranberry (*Willstätter, Everest*, Ann. **401**, 227; *Willstätter*, Ann. **408**, 12). **Peonidin chloride**, *3,5,7,4′-tetrahydroxy-3′-methoxyflavylium chloride*, from the peony (*Willstätter*, Ann. **408**, 136; *Karrer, Widmer*, Helv. **10**, 8). **Delphinidin chloride**, *3,5,7,3′,4′,5′-hexahydroxyflavylium chloride*, m.p. over 350°, from larkspur (*Willstätter*, Ann. **408**, 78; *Karrer, Schwarz*, Helv. **11**, 916), whortleberry, grape, mallow (*Karrer, Widmer*, Helv. **10**, 5), and gentian (*Karrer, Widmer*, Helv. **10**, 67). **Syringidin chloride**, *3,5,7,4′-tetrahydroxy-3′,5′-dimethoxyflavylium chloride*, from the blue grape, the mallow, the cyclamen, and whortleberry (*Karrer, Widmer*, Helv. **10**, 5). **Hirsutidin chloride**, *3,5(or 7),4′-trihydroxy-7(or 5),3′,5′-trimethoxyflavylium chloride*, from *Primula hirsuta* (*Karrer et al.*, Helv. **10**, 758).

For other anthocyans or anthocyanidins, see *Karrer et al.*, Helv. **10**, 67, 758.

These anthocyanidin chlorides are mostly red substances, which are converted by alkali to the violet to blue pigment bases; the latter isomerize quickly to colorless pseudo-bases. It is remarkable that the same pigment is contained in the red rose and the blue cornflower; the different shades are functions of the hydrogen ion concentration of the cell sap (see also *Karrer et al.*, Helv. **10**, 742).

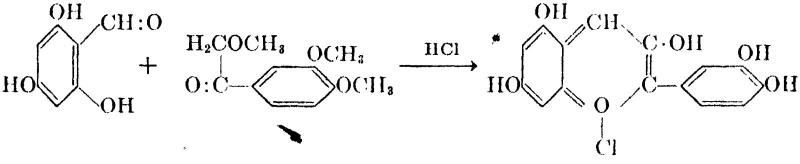
Synthesis of the Anthocyanidins.—The constitution of the flower pigments has been proved by the complete synthesis of the anthocyanidins. The older methods used the synthesis of flavylium chloride given on p. 181, with phloroglucinaldehyde as the aldehyde. This necessitates subsequent introduction of the 3-hydroxyl group (*Willstätter*, *Mallison*, Sitz.-ber.kgl.preuss.Akad.Wiss., **1914**, 769).

It is better to introduce this hydroxyl group at the beginning, as *Willstätter* (Ber. **57**, 1938) did in the synthesis of cyanidin iodide:


Phloroglucin-aldehyde
Methoxyacetic acid
Perkin reaction
Trimethoxycoumarin (after methylation with diazomethane)
Veratryl-magnesium iodide
Pentamethyl ether of the cyanidin pseudo-base
HI, d 1.7

Cyanidin iodide
(Identical with the compound from the rose: *Robinson*, *Willstätter*, Ber. **61**, 2504; *Kuhn* *Wagner-Jauregg*, Ber. **61**, 2506)

Another important synthesis of the anthocyanidin group was developed by *Robinson* and *Pratt* (J. **127**, 166, 1128). They used α-methoxyacetophenone derivatives in the flavylium synthesis given on p. 181:

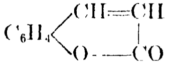


Phloroglucinaldehyde **4-Methoxyacetoveratrole** Cyanidin chloride

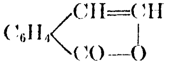
For the synthesis of anthocyans with the sugar radical in the 4′-position, see *Robertson, Robinson*, J. **1926**, 1713.

For the synthesis of spiropyrans, see *Löwenbein, Katz*, Ber. **59**, 1377; *Dilthey, Wübken*, Ber. **61**, 963.

The **COUMARINS** (I) and **ISOCOUMARINS** (II) are **benzo derivatives** of 1,2-**pyrone**. The isocoumarins can be converted by NH_3 with equal ease into benzopyridones or hydroxyisoquinoline derivatives, which is analogous to the conversion of the pyrones to pyridones.

(I) 

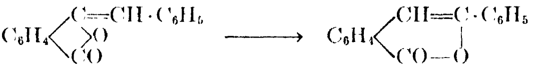
$$C_6H_4\left\langle\begin{matrix}CH{=}CH\\ |\\ O{-}{-}CO\end{matrix}\right.$$

 (II)

$$C_6H_4\left\langle\begin{matrix}CH{=}CH\\ |\\ CO{-}O\end{matrix}\right.$$

Coumarin and its homologues have been treated in Vol. III as the lactones of *o*-hydroxycinnamic acids.

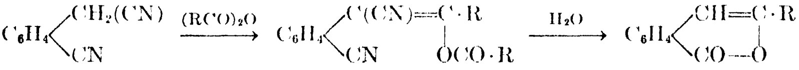
Isocoumarins, the lactones of *o*-β-hydroxyvinylbenzoic acids, are usually prepared by the following methods: (*1*) Benzylidene- and alkylidenephthalides can be rearranged into isobenzylidenephthalides or isocoumarins (*Pinner*, Ber. **20**, 2363; *Ruhemann*, Ber, **24**, 3973):



$$C_6H_4\left\langle\begin{matrix}C{=}CH\cdot C_6H_5\\ \rangle O\\ CO\end{matrix}\right. \longrightarrow C_6H_4\left\langle\begin{matrix}CH{=}C\cdot C_6H_5\\ |\\ CO{-}O\end{matrix}\right.$$

Benzylidenephthalide Phenylisocoumarin

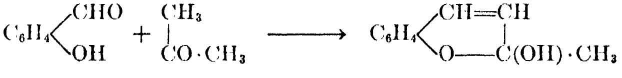
(*2*) Isocoumarins are formed by the hydrolysis with acids of the condensation products of acid anhydrides or chlorides and *o*-cyano-α-toluunitrile; one cyano group is split off, and the other is hydrolyzed (*Gabriel, Neumann*, Ber. **25**, 3566; *Gabriel, Posner*, Ber. **27**, 827):



$$C_6H_4\left\langle\begin{matrix}CH_2(CN)\\ CN\end{matrix}\right. \xrightarrow{(RCO)_2O} C_6H_4\left\langle\begin{matrix}C(CN){=}C\cdot R\\ \qquad\quad |\\ CN \qquad OCO\cdot R\end{matrix}\right. \xrightarrow{H_2O} C_6H_4\left\langle\begin{matrix}CH{=}C\cdot R\\ |\\ CO{-}O\end{matrix}\right.$$

Coumarinaldehydes are obtained by the *Reimer-Tiemann* method (*Sen, Chakravarty*, Am. **50**, 2428).

BENZOPYRANOLS. Benzopyranols, which contain the grouping $>C\left\langle\begin{matrix}OH\\ R\end{matrix}\right.$ in place of the >CO-group of benzopyrone, are produced by condensation of *o*-hydroxybenzaldehydes and ketones by means of acids; they are the pseudo-bases of the benzopyrylium compounds described above.

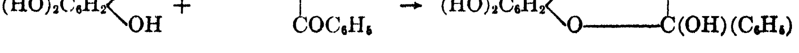


$$C_6H_4\left\langle\begin{matrix}CHO\\ OH\end{matrix}\right. + \begin{matrix}CH_3\\ |\\ CO\cdot CH_3\end{matrix} \longrightarrow C_6H_4\left\langle\begin{matrix}CH{=}CH\\ |\\ O{-}{-}C(OH)\cdot CH_3\end{matrix}\right.$$

The simplest benzopyranols are unstable compounds. With mineral acids and metal halides, like xanthydrol and phenylxanthenol (p. 189), they form highly colored salt-like compounds, some of which are very stable (*Decker, v. Fellenberg*, Ann. **364**, 17; *Gomberg, Cone*, Ann. **370**, 196).

2-Phenyl-2-benzopyranol, from acetophenone and salicylaldehyde, is converted back to its components by aqueous sodium hydroxide. **2,3-Diphenyl-2-benzopyranol**, m.p. 122°, from salicylaldehyde and desoxybenzoin.

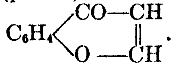
Among the benzopyranols are those dyestuffs which result from the condensation of polyhydric phenols, such as resorcinol, pyrogallol, phloroglucinol, and hydroxyhydroquinone, with β-diketones:



$$(HO)_2C_6H_2\left\langle\begin{matrix}H\\ OH\end{matrix}\right. + \begin{matrix}C_6H_5\cdot CO\cdot CH_2\\ |\\ COC_6H_5\end{matrix} \rightarrow (HO)_2C_6H_2\left\langle\begin{matrix}C(C_6H_5){:}CH\\ |\\ O{-}{-}{-}C(OH)(C_6H_5)\end{matrix}\right.$$

Dyes such as phenacetein, resacetein, and orcacetein, which are prepared together with hydroxyacetophenones (Vol. III, p. 351) by the action of acetic anhydride and zinc chloride on phenols, are also benzopyranols (*Bülow, Wagner*, Ber. **34**, 1189; **36**, 1941; *Bülow, v. Sicherer*, Ber. **34**, 2368; *Bülow, Grotowsky*, Ber. **35**, 1799; *Bülow, Riess*, Ber. **36**, 3607; *Bülow, Sautermeister*, Ber. **37**, 354; *Bülow, Deiglmayr*, Ber. **37**, 1791; *Bülow, Schmid*, Ber. **39**, 850).

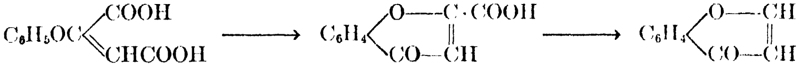
BENZO- and **DIBENZO-1,4-PYRONE** are the parent compounds of a large number of yellow plant pigments (*v. Kostanecki*), some of which resemble the simple 1,4-pyrones (p. 179) in forming salt-like compounds with acids.

1,4-Benzopyrone, 

$$C_6H_4{<}\begin{matrix}CO-CH\\ \|\\ O-CH\end{matrix}$$

. The parent compound of this group is also called **chromone,** while the 2-phenyl derivative is known as flavone. Chromones and flavones are obtained:

(*1*) From their 2-carboxylic acids, which result from the condensation of phenoxyfumaric acids in the presence of sulfuric acid (*Ruhemann, Stapleton*, J. **77**, 1179; *Ruhemann, Bausor*, J. **79**, 470; *Ruhemann, Wragg*, J. **79**, 1185):

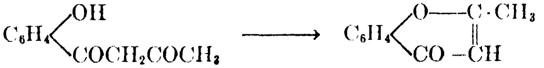


$$C_6H_5OC{<}\begin{matrix}COOH\\ CHCOOH\end{matrix} \longrightarrow C_6H_4{<}\begin{matrix}O-C\cdot COOH\\ \|\\ CO-CH\end{matrix} \longrightarrow C_6H_4{<}\begin{matrix}O-CH\\ \|\\ CO-CH\end{matrix}$$

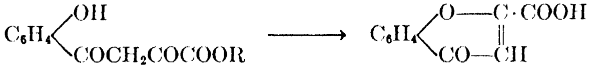
Chromone

From β-phenoxycinnamic acid ester, 2-phenylchromone or flavone is obtained (*Ruhemann*, Ber. **46**, 2188; **54**, 912).

(*2a*) 2-Alkyl- or 2-arylchromones or 2-chromonecarboxylic acids are prepared from *o*-hydroxybenzoyl-β-ketones and *o*-hydroxybenzoylpyruvic acid esters:

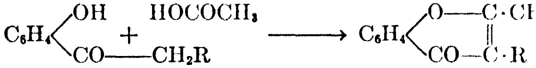


$$C_6H_4{<}\begin{matrix}OH\\ COCH_2COCH_3\end{matrix} \longrightarrow C_6H_4{<}\begin{matrix}O-C\cdot CH_3\\ \|\\ CO-CH\end{matrix}$$



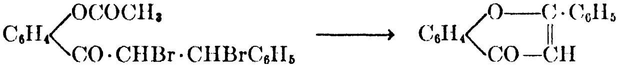
$$C_6H_4{<}\begin{matrix}OH\\ COCH_2COCOOR\end{matrix} \longrightarrow C_6H_4{<}\begin{matrix}O-C\cdot COOH\\ \|\\ CO-CH\end{matrix}$$

(*2b*) A similar synthesis consists in the treatment of *o*-hydroxyacetophenone and homologous ketones with acetic anhydride (*Wittig, Bangert*, Ber. **58**, 2627, 2636; *Wittig*, Ann. **446**, 155):



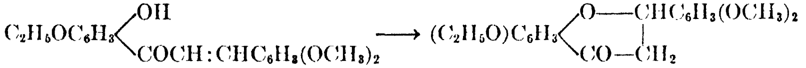
$$C_6H_4{<}\begin{matrix}OH & HOCOCH_3\\ & +\\ CO- & CH_2R\end{matrix} \longrightarrow C_6H_4{<}\begin{matrix}O-C\cdot CH_3\\ \|\\ CO-C\cdot R\end{matrix}$$

(*3*) Flavone (*2-phenylchromone*) is also formed from benzylidene-*o*-acetoxyacetophenone dibromide with alkali:



$$C_6H_4{<}\begin{matrix}OCOCH_3\\ CO\cdot CHBr\cdot CHBrC_6H_5\end{matrix} \longrightarrow C_6H_4{<}\begin{matrix}O-C\cdot C_6H_5\\ \|\\ CO-CH\end{matrix}$$

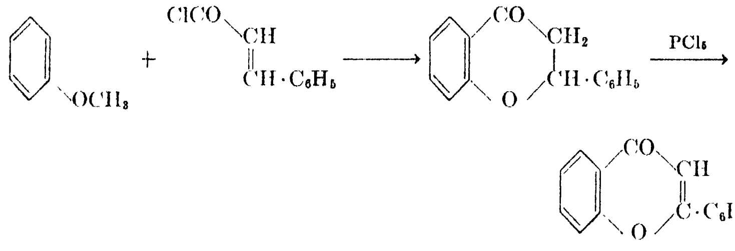
Substituted benzylidene-*o*-hydroxyacetophenones condense partially during their preparation and partially when treated with hydrochloric acid or aqueous sodium hydroxide to dihydroflavones or flavanones (*Löwenbein*, Ber. **57**, 1515):

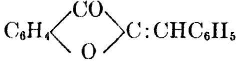


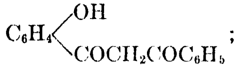
$$C_2H_5OC_6H_3{<}\begin{matrix}OH\\ COCH:CHC_6H_3(OCH_3)_2\end{matrix} \longrightarrow (C_2H_5O)C_6H_3{<}\begin{matrix}O-CHC_6H_3(OCH_3)_2\\ |\\ CO-CH_2\end{matrix}$$

3-Ethoxy-3′,4′-dimethoxyflavanone

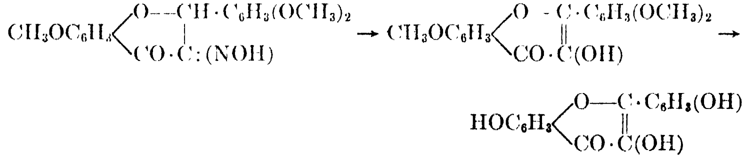
(*4*) A method especially adapted for the preparation of flavanones (2,3-dihydroflavones) and flavones comprises the reaction of cinnamic acid chloride (for flavanones) or of phenylpropiolic acid chloride (for flavones) with the methyl ethers of phenols in the presence of aluminum chloride (*Simonis*, Z.Angew.Chem. **39**, 1461):



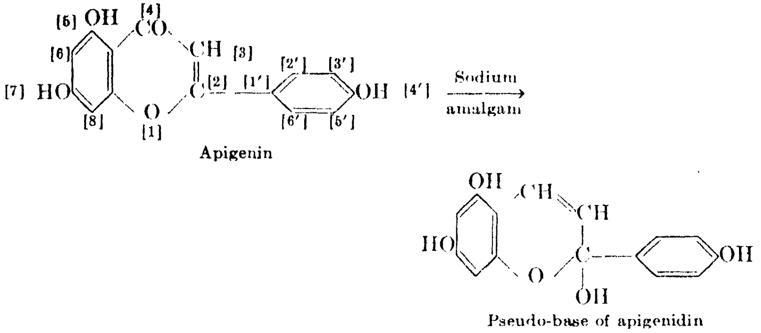
When treated with bromine and alkali, some substituted benzylidene-*o*-hydroxyacetophenones are converted to flavones (*Blumstein, v. Kostanecki,* Ber. **33**, 1478); others, when their dibromides are treated with alkali, give in place of the flavones the isomeric benzylidenecoumaranones:  $C_6H_4\langle{}^{CO}_{O}\rangle C{:}CHC_6H_5$ (see page 55) (*Emilewicz, v. Kostanecki,* Ber. **32**, 309). The dibromides of the benzylidenecoumaranones rearrange in alkaline medium under certain conditions into flavonols (formula, p. 188) (*Auwers, Müller,* Ber. **41**, 4233). The course taken by this reaction depends on various reaction conditions and on the substituents present in the benzene ring (see the systematic investigations of *v. Auwers, Anschütz,* Ber. **54**, 1543; also *Röthlisberger,* Helv. **8**, 112).

When heated with alkali the flavones are first split into *o*-hydroxyphenyl-β-diketones, such as  $C_6H_4\langle{}^{OH}_{COCH_2COC_6H_5}$; further decomposition proceeds in two directions: into acetophenone and *o*-hydroxybenzoic acid, and into *o*-hydroxyacetophenone and benzoic acid (*Kostanecki, Tambor,* Ber. **33**, 330). Hydroxyflavones and hydroxyflavonols, of which many are known (*Berstein, Fraschina, v. Kostanecki,* Ber. **38**, 2177), generally dye alumina mordants yellow (*Bonifazi, v. Kostanecki, Tambor,* Ber. **39**, 86).

A series of plant pigments are derived from flavone (see p. 187). The derivatives of 3-*hydroxyflavone, flavonol,* are better known. The introduction of the OH group in the 3-position during the synthesis of the flavonol dyes, fisetin, quercetin, and kaempferol, takes place after the formation of the flavanone ring-system. With N_2O_3 these flavanones yield isonitroso compounds, which decompose on hydrolysis into hydroxylamine and flavonols. The following equations give these reactions for fisetin:

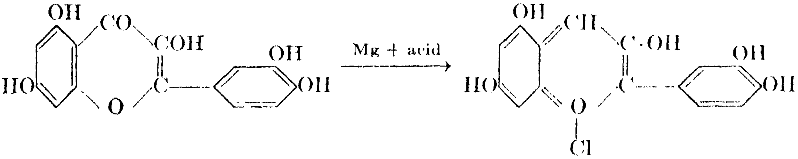

Fisetin

Relation of Flavone and Flavonol Dyes to Benzopyrylium Compounds and Anthocyanidins.—If the formulas of the flavone dyestuffs or of the flavonols are compared with those of the benzopyrylium compounds or anthocyanidins, it is apparent that the latter are reduction products of the former. This has been verified experimentally by the conversion of flavone dyes to derivatives of *benzopyrylium* (*Asahina, Inubuse,* Ber. **61**, 1646) with sodium amalgam, and of *quercetin,* as an example of a flavonol dye, into *cyanidin chloride* with magnesium and acid (*Willstätter, Mallison,* Ann. **408**, 27; Sitz.-ber.kgl.preuss.Akad.Wiss. **1914**, 769; *Willstätter,* Ber. **47**, 2874). Probably in the plants the flavones or flavonols are the forerunners of the flower pigments [*cf. Noack,* Z.Botan. **14 (1923)**, 1; *Karrer, Schwarz,* Helv. **11**, 916]. The following equations illustrate these transitions:



Apigenin

Pseudo-base of apigenidin

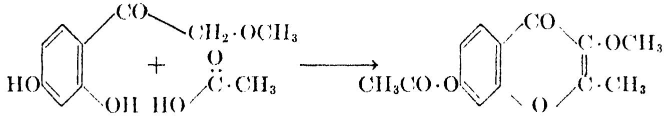


Quercetin

Cyanidin chloride

1,4-**Benzopyrone**, *chromone*, m.p. 59°, is obtained by heating its 2-carboxylic acid, m.p. 251° (dec.), which is prepared from phenoxyfumaric acid with concentrated H_2SO_4 and from *o*-hydroxybenzoylpyruvic acid with hydrochloric acid (see above). 2-**Methylchromone**, m.p. 71°, from 1-*o*-methoxybenzoylacetone with hydriodic acid by method *2* (see above). Many **hydroxychromones** have been prepared by similar reactions (*cf.* the summary by *Heywang, v. Kostanecki*, Ber. **35**, 2890). The methyl group in the 2-position is very reactive, like the methyl group in quinaldine. A 3,7-**dihydroxychromone** is formed by the action of air on an alkaline solution of brasilin.

Chromonols (*3-hydroxychromones*) are obtained from 2,4-dihydroxy-ω-methoxyacetophenone with acetic anhydride and sodium acetate (*Allan, Robinson*, J. **125**, 2192):

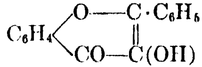
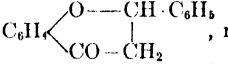


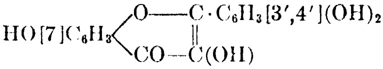
2,7-Dihydroxychromone, m.p. 249° (dec.).

The 2-phenyl derivatives of 3-hydroxychromone, the flavonols (see p. 188), are more important than the 2-alkyl-3-hydroxychromones.

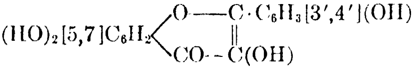
Flavone, *2-phenyl-1,4-benzopyrone*, *2-phenylchromone*, m.p. 97°, from benzal-*o*-acetoxyacetophenone dibromide and from 1-*o*-hydroxyphenyl-1,3-butanedione. The farinaceous covering of certain types of *Primula* is almost pure flavone. For derivatives of 3-phenylchromone (*isoflavone*) see *Bargellini, Monti*, Atti accad. Lincei [6] **8**, 395; *Baker, Pollard, Robinson*, J. **1929**, 1468. **Chrysin**, *5,7-dihydroxyflavone* (for the numbering of substituents, see above), m.p. 275°, occurs in the buds of various types of poplars and is synthesized by boiling the condensation product of phloroacetophenone trimethyl ether, benzoic ester, and sodium ethylate with hydriodic acid (*Emilewicz, v. Kostanecki, Tambor*, Ber. **32**, 2448; *v. Kostanecki, Lampe*, Ber. **37**, 3167). **Apigenin**, *5,7,4'-trihydroxyflavone*, m.p. 347°, occurs as the glucoside *apiin* in parsley and celery, and is synthesized from the condensation product of phloroacetophenone trimethyl ether and anisic acid ester (*Wahl*, Ber. **33**, 1988; *Vongerichten*, Ber. **33**, 2334; Ann. **318**, 121; *Breyer, v. Kostanecki*, Ber. **38**, 931). **Luteolin**, *5,7,3',4'-tetrahydroxyflavone*, m.p. 329°, the yellow pigment of weld, *Reseda luteola* (*cf.* Vol. III, p. 578), is prepared by condensation of phloroacetophenone trimethyl ether and veratric acid ester (*v. Kostanecki, Różycki, Tambor*, Ber. **33**, 3410; *Diller, v. Kostanecki*, Ber. **34**, 1449; *Fainberg, v. Kostanecki*, Ber. **37**, 2625).

For aminoflavones see *Bogert, Marcus*, Am. **41**, 83.

The following pigments are derived from 3-**flavonol**,  $C_6H_4\left\langle\begin{array}{l} O - C\cdot C_6H_5 \\ \qquad \| \\ CO - C(OH)\end{array}\right.$ bright yellow needles, m.p. 170°, which is obtained by hydrolytic fission of the isonitroso derivative of **flavanone**,  $C_6H_4\left\langle\begin{array}{l} O - CH\cdot C_6H_5 \\ \qquad | \\ CO - CH_2\end{array}\right.$, m.p. 76°, prepared by boiling *o*-hydroxybenzylidene-acetone with hydrochloric acid (*v. Kostanecki, Szabrański*, Ber. **37**, 2819; formula, p. 186). The following are also called anthoxanthins. **Galangin**, 5,7-*dihydroxy-3-flavonol*, m.p. 218°, is found together with kaempferol (see below) in the *galanga* root; synthesis: *v. Kostanecki, Lampe, Tambor*, Ber. **37**, 2803. **Kaempferol**, 5,7,4′-*trihydroxy-3-flavonol*, m.p. 274°, is a constituent of the *galanga* root and also occurs as the rhamnoside *kaempferitrin*, $C_{27}H_{30}O_{14}$, in Java indigo (*Perkin*, J. **91**, 435) and as the glucoside *robinin* in the leaves of *Robinia pseudacacia* (*Waliaschko*, Arch.Pharm. **247** (1909), 447] (synthesis: *v. Kostanecki, Lampe, Tambor*, Ber. **37**, 2096; *cf. Testoni*, Gazz. **30**, II, 327). **Fisetin** (I), m.p. 330°, and **quercetin** (II), m.p. 314°; the constitution of these pigments, of which the former is obtained from the young fustic of *Rhus cotinus* and from the wood of *quebracho Colorado* (*Perkin, Hummel*, J. **69**, 1295), and the latter is obtained from quercitrin (Vol. III, p. 578), the glucoside of the bark of *quercus tinctoria*, was determined from their decomposition products and by synthesis (see above and *v. Kostanecki, Lampe, Tambor*, Ber. **37**, 1402; *v. Kostanecki, Nitkowski*, Ber. **38**, 3587). **Morin**, 5,7,2′,4′-*tetrahydroxy-3-flavonol*, m.p. 290°, from *Morus tinctoria*, is synthesized from the condensation product of 2,4-dimethoxybenzaldehyde with phloroacetophenone dimethyl ether (*v. Kostanecki, Lampe, Tambor*, Ber. **39**, 625) or from ω-methoxyphloroacetophenone with 2,4-dimethoxybenzoic acid anhydride (*Robinson, Venkataraman*, J. **1929**, 61). **Myricetin**, 5,7,3′,4′,5′-*pentahydroxy-3-flavonol*, m.p. 355–360°, is a yellow dye obtained from the bark of *Myrica nagi* (*Perkin*, J. **81**, 203). For other yellow dyes of this group, such as **vitexin** from *Vitex littoralis* and **scoparin** from gorse and *Spartium scoparium*, see *Perkin, Wood*, Proc.Chem.Soc. **1897/-1898**, No. 190, 56; *Perkin, ibid.* **1898/1899**, No. 198, 183; **15**, 123; *Molisch, Goldschmidt*, Mo. **22**, 679.

(I) 

$$HO[7]C_6H_3\left\langle\begin{array}{l} O - C\cdot C_6H_3[3',4'](OH)_2 \\ \qquad \| \\ CO - C(OH)\end{array}\right.$$

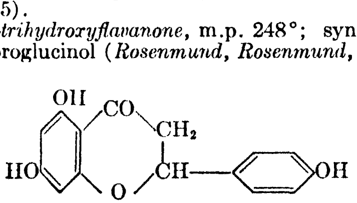
 (II)

$$(HO)_2[5,7]C_6H_2\left\langle\begin{array}{l} O - C\cdot C_6H_3[3',4'](OH)_2 \\ \qquad \| \\ CO - C(OH)\end{array}\right.$$

For a series of new syntheses of flavones and flavonols, see *Kalff, Robinson*, J. **127**, 1968; *Robertson, Robinson*, J. **1926**, 1713; **1927**, 242, 1710; *Robinson et al.*, J. **1926**, 1951, 1959, 1968, 2334, 2336, 2344; *Pratt, Robertson, Robinson*, J. **1927**, 1975.

Derivatives of *flavanone* are also found in nature. They were formerly thought to be hydroxychalcone derivatives, but have since been identified as flavanones. The flavanone ring readily opens, producing isomeric hydroxychalcones (*Asahina, Inubuse*, Ber. **61**, 1515).

Naringenin, 5,7,4′-*trihydroxyflavanone*, m.p. 248°; synthesis from *p*-cumaric acid chloride and phloroglucinol (*Rosenmund, Rosenmund*, Ber. **61**, 2608).



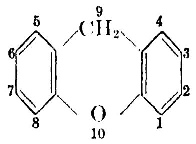
Naringenin

Sakuranetin is the 7-monomethyl ether of naringenin (synthesis: *Asahina, Shinoda, Inubuse,* J.Pharm.Soc.Japan **1927**, 133).. **Hesperitin**, 5,7,3'-*trihydroxy-4'-methoxyflavanone*, m.p. 224°, is obtained by fission of the glucoside hesperidin. **Homoeriodictyol**, 5,7,4'-*trihydroxy-3'-methoxyflavanone*, m.p. 223°; **eriodictyol**, 5,7,3',4'-*tetrahydroxyflavanone*, m.p. 267°, both from the leaves of *Eriodictyon californicum*.

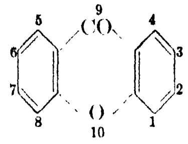
(c) Dibenzopyrans and Dibenzopyrones

The xanthenes and xanthones are dibenzopyrans and dibenzopyrones:

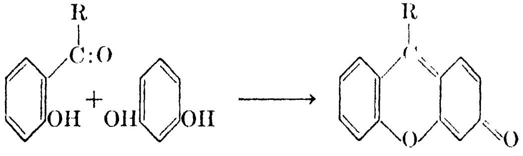
Xanthene:



Xanthone:

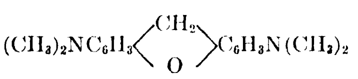


Xanthenes are usually obtained by reduction of the easily obtained xanthones. A comprehensive ring-synthesis is known only for the hydroxyxanthenes. It consists in the action of acid condensing agents on a mixture of aromatic *o*-hydroxy aldehydes or ketones and polyhydric phenols:

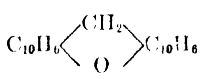


Xanthene, colorless, m.p. 99°, b.p. 312°, is prepared by reduction of xanthone and hydroxyxanthones; when fused with KOH it gives *o*-dihydroxybenzophenone. 3,6-**Dimethylxanthene**, *α-pyrocresol*, m.p. 196°, occurs in coal tar (*Zmerzlikar*, Mo. **31**, 897). 9-**Phenylxanthene**, m.p. 145°, by reduction of phenylxanthenol (see below). 9,9-**Diphenylxanthene**, m.p. 200°, from *o*-phenoxytriphenylmethanol by elimination of water (*Ullmann, Engi*, Ber. **37**, 2367). Phenylxanthenes occur in coal tar [*Russig*, Z.angew.Chem. **32** (1919), 37; *Marcusson, ibid.* **32**, 385]. **Tetramethyldiaminoxanthene** (I), m.p. 116°, from tetramethyldi-

(I)



$(CH_3)_2NC_6H_3{<}\genfrac{}{}{0pt}{}{CH_2}{O}{>}C_6H_3N(CH_3)_2$



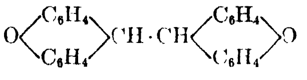
$C_{10}H_6{<}\genfrac{}{}{0pt}{}{CH_2}{O}{>}C_{10}H_6$

(II)

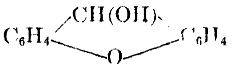
aminodihydroxydiphenylmethane with H_2SO_4, is the leuco base of the dye pyronine (*Bucherer, Grolée*, Ber. **39**, 993). **Dinaphthoxanthene** (II), m.p. 199°, is formed by the condensation of formaldehyde with 2-naphthol (*Wolff*, Ber. **26**, 84). **Octahydroxanthenedione**, m.p. 163°, is prepared from methylene-*bis*-hydroresorcinol with acetic anhydride (*Vorländer*, Ann. **309**, 348).

Dixanthyl (III), m.p. 205°, and its 9,9'-dialkyl derivatives are obtained from xanthydrol by treatment with VCl_2 or VCl_4 in strong hydrochloric acid (*Conant, Garvey*, Am. **49**, 2080). They dissociate more or less readily into highly colored free xanthyl radicals (*loc. cit*). The same type of dissociation has been found with dixanthyl-9,9'-dicarboxylic acid.

(III)



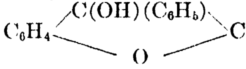
$O{<}\genfrac{}{}{0pt}{}{C_6H_4}{C_6H_4}{>}CH\cdot CH{<}\genfrac{}{}{0pt}{}{C_6H_4}{C_6H_4}{>}O$



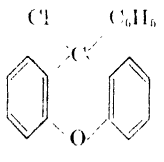
$C_6H_4{<}\genfrac{}{}{0pt}{}{CH(OH)}{O}{>}C_6H_4$

(IV)

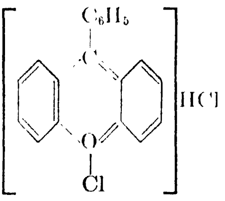
Xanthydrol (IV), 9-*hydroxyxanthene*, m.p. 124° (not sharp), is prepared by careful reduction of xanthone; it is an unstable substance which, like benzhydrol (Vol.

III, p. 512), has a great tendency toward loss of water and formation of its ether, *xanthydrol ether*, $(C_{13}H_9O)_2O$, m.p. 200° (*Meyer, Saul*, Ber. **26**, 1276). With urea xanthydrol forms a very sparingly soluble *dixanthylurea*, m.p. about 260° (dec.), which is suitable for the quantitative determination of urea in very small amounts [*Iwanoff*, Z.physiol.Chem. **170**, 276; Biochem.Z. **135** (1923), 6]. **Dibenzoxanthydrol**, $HOCH(C_{10}H_6)_2O$, is present in the reaction products of chloroform and alkali on 2-naphthol (*Fosse*, Bull. [3] **27**, 496; *Gomberg, Cone*, Ann. **376**, 195). **9-Phenylxanthydrol**,  $C_6H_4{<}\overset{C(OH)(C_6H_5)}{\underset{O}{\qquad}}{>}C_6H_4$, m.p. 158°, from xanthone and C_6H_5MgBr.

Xanthydrol, dibenzoxanthydrol and, to a greater degree, 9-phenylxanthydrol show the same abnormal mobility of the hydroxyl group as triphenylmethanol. The OH group can easily be replaced by Cl and Br. The chloride and bromide, which are colorless in the solid state, correspond to the colorless triphenylmethyl halides; with excess mineral acid or metal halide they form highly colored double salts. As in the case of triphenylmethanol, the sulfate and perchlorate of xanthydrol are highly colored in the solid state. The uncolored salt-like compounds are probably derived from xanthene, while the colored double-compounds with mineral acids and heavy metal salts are derived from the *o*-quinoid xanthylium structure:



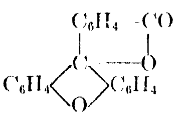
Colorless



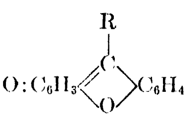
Red

The parallelism of 9-phenylxanthydrol with triphenylmethanol is also evident in the formation of the free radical *9-phenylxanthyl* by elimination of the halogen from 9-phenylxanthydrol chloride with molecular silver in benzene solution, giving a deep red solution, from which the radical can be isolated (*Schlenk*, Ann. **394**, 188). *Bis*-(9-**phenylxanthyl)peroxide**, colorless, m.p. about 220°.

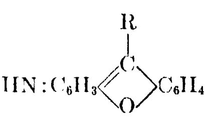
The **fluorans, fluorones,** and **fluorimes** are related to the xanthydrols (*Möhlau, Koch*, Ber. **27**, 2887):


$C_6H_4{<}\overset{\overset{C_6H_4-CO}{|\qquad|}}{\underset{O}{C\!-\!O}}{>}C_6H_4$

Fluoran

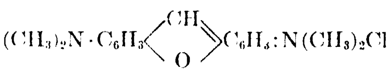

$O{:}C_6H_3{<}\overset{\overset{R}{|}}{\underset{O}{C}}{>}C_6H_4$

Fluorones


$HN{:}C_6H_3{<}\overset{\overset{R}{|}}{\underset{O}{C}}{>}C_6H_4$

Fluorimes

These are the parent substances of the fluorescein, rosamine, and rhodamine dyes, and have been partially described in connection with them. Among the fluorimes is **pyronine**, a dye which is obtained from dihydroxytetramethyldiaminodiphenylmethane by elimination of water and oxidation; the leuco derivative of


$(CH_3)_2N\cdot C_6H_3{<}\overset{CH}{\underset{O}{\quad}}{>}C_6H_3{:}N(CH_3)_2Cl$

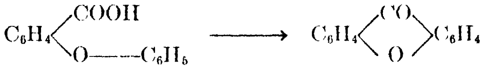
Pyronine

pyronine is tetramethyldiaminoxanthene (p. 189). When oxidized in alkaline solution pyronine gives **tetramethyldiaminoxanthone**, m.p. 241°. Pyronine dyes silk and mordanted cotton a beautiful shade of rose (*Möhlau, Koch*, Ber. **27**, 2896; *Biehringer*, Ber. **27**, 3304; J.pr. **54**, 217).

Xanthones

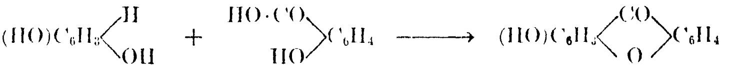
9-OXOXANTHENES, XANTHONES, are prepared by the following general methods:

(*1*) From arylsalicylic acids by elimination of water (*Ullmann, Zlokasoff,* Ber. **38,** 2111; *Ullmann, Wagner,* Ann. **355,** 359):



$$C_6H_4\begin{matrix}COOH\\O-C_6H_5\end{matrix} \longrightarrow C_6H_4\begin{matrix}CO\\O\end{matrix}C_6H_4$$

(*2*) By condensation of salicylic acid and phenols with H_2SO_4, acetic anhydride, and the like (*Graebe,* Ber. **21,** 502; *cf. Strohback,* Ber. **34,** 4136):



$$(HO)C_6H_3\begin{matrix}H\\OH\end{matrix} + \begin{matrix}HO\cdot CO\\HO\end{matrix}C_6H_4 \longrightarrow (HO)C_6H_3\begin{matrix}CO\\O\end{matrix}C_6H_4$$

Resorcinol Salicylic acid Hydroxyxanthone

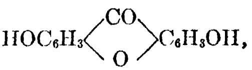
(*3*) By distillation of orthophosphoric acid esters of phenols with potassium carbonate (*Fosse,* C.r. **136,** 1006).

XANTHONE, $C_{13}H_8O_2$, m.p. 174°, b.p. 250°, is obtained from phenyl salicylate or phenylsalicylic acid (Vol. III, p. 357) with concentrated H_2SO_4, from phenyl phosphate and potassium carbonate by distillation, from 2,2′-diaminobenzophenone with nitrous acid (*Staedel,* Ber. **27,** 3363), and from fluoran and hydrofluoranic acid (Vol. III, p. 544) by distillation with lime (*Meyer, Hoffmeyer,* Ber. **25,** 2119). By careful fusion with KOH it is opened to dihydroxybenzophenone (Vol. III, p. 521). As benzophenone gives tetraphenylethylene (Vol. III, p. 574), so xanthone is converted by treatment with zinc dust, hydrochloric acid, and glacial acetic acid into 9-xanthylidenexanthene, $O(C_6H_4)_2C:C(C_6H_4)_2O$, m.p. 315° (*Gurgenjanz, v. Kostanecki,* Ber. **28,** 2311). Like the flavones the xanthones do not react directly with hydroxylamine and phenylhydrazine; however, 2,2′-dihydroxybenzophenone and aniline give **xanthone anil,** $O(C_6H_4)_2$-$C:NC_6H_5$, m.p. 134°, converted by H_2S to **xanthione, thioxanthone,** $O(C_6H_4)_2CS$, m.p. 156°; the latter with hydroxylamine and phenylhydrazine yields **xanthone oxime,** $O(C_6H_4)_2C:NOH$, m.p. 161°, and **xanthone phenylhydrazone,** m.p. 152° (*Graebe, Röder,* Ber. **32,** 1688).

Hydroxyxanthones, $C_{13}H_7(OH)O_2$; all four possible isomers are obtained by condensation of salicylic acid with resorcinol, hydroquinone, and pyrocatechol (*v. Kostanecki, Rutishauser,* Ber. **25,** 1652; *Dreher, v. Kostanecki,* Ber. **26,** 71).

Dihydroxyxanthones: **1,3-dihydroxyxanthone,** m.p. 259° (*Nishikawa, Robinson,* J. **121,** 839).

EUXANTHONE, 3,5-DIHYDROXYXANTHONE,



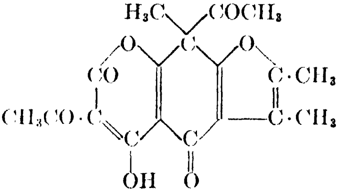
$$HOC_6H_3\begin{matrix}CO\\O\end{matrix}C_6H_3OH,$$

yellow needles, m.p. 237° (sublimable), occurs free and in combination with glucuronic acid as *euxanthinic acid* [*Neuberg, Neimann,* Z.physiol.Chem. **44** (1905), 114] in *Indian yellow,* which is formed in the urine of cows after ingestion of the leaves of *Mangifera indica.* The mother substance is *mangin* [*Wiechowski,* Arch. exptl.Path.Pharm. **97** (1923), 462]. Euxanthone has been synthesized by condensation of equimolar proportions of β-resorcylic acid and hydroquinonecarboxylic acid with $(CH_3CO)_2O$ (*v. Kostanecki, Nessler,* Ber. **24,** 3982; *v. Kostanecki,* Ber. **27,** 1989; *Graebe,* Ber. **33,** 3360; Ann. **254,** 265; *Ullmann, Panchaud,* Ann. **350,** 108). **2,7-Dihydroxyxanthone,** from 2,2′,4,4′-tetrahydroxybenzophenone (a fission product in the alkali fusion of fluorescein chloride) by heating, forms colorless needles and shows a strong violet-blue fluorescence in alkaline solution (*Meyer, Conzetti,* Ber. **30,** 969). **1,8-Dihydroxyxanthone** and **3,6-dihydroxyxanthone** (*Baeyer,* Ann. **372,** 131, 139). **2,4,6-Trihydroxyxanthone, gentisein,** $C_{13}H_5(OH)_3O_2(+2H_2O)$; m.p. 315°, is synthesized from hydroquinonecarboxylic acid and phloroglucinol; it dyes mordanted cotton bright yellow. Its monomethyl ether is **gentisin,** which occurs in the root of *Gentiana lutea* (*v. Kosta-*

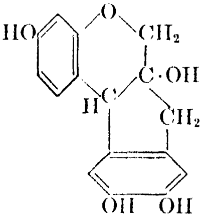
necki, Tambor, Mo. **15,** 1; *Dickinson, Heilbron,* J. **1927,** 1699). **Dibenzoxanthones** and **benzoxanthenes**: *Schmidlin, Huber,* Ber. **43,** 2825.
Nitroxanthones: *Dhar,* J. **117,** 1053.

(d) More Complicated Pyran and Pyrone Derivatives

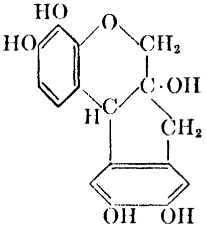
USNINIC ACID, $C_{18}H_{16}O_7$ (*Schöpf,* Ann. **459,** 233), which is present in many lichens, has been found to be a derivative of coumarin, having the constitution:



BRASILIN, $C_{16}H_{14}O_5$, present in redwood, and **HEMATOXYLIN,** $C_{16}H_{14}O_6$, present in logwood, contain a pyran ring. Hematoxylin is a hydroxyl derivative of brasilin, as the following formulas show:

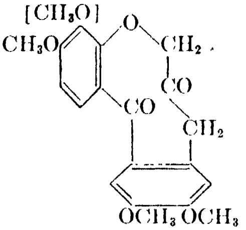


Brasilin



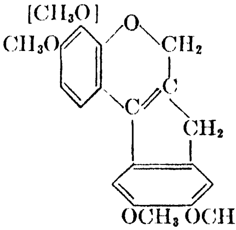
Hematoxylin

These structures have been assigned to these compounds on the basis of their oxidative degradation (*a*) with the oxygen of the air in alkaline solution to 3,7-dihydroxychromone and 3,7,8-trihydroxychromone, respectively, and (*b*) of their permethylated products to:



Trimethylbrasilon
(or tetramethylhematoxylon)

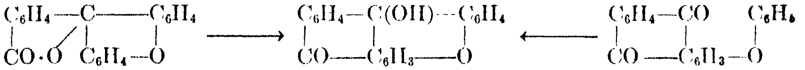
which is reduced by phenylhydrazine to



Trimethylanhydrobrasilin
(or tetramethylanhydrohematoxylin)

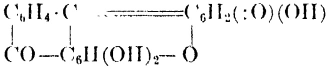
The constitution of the latter compound has been proved by synthesis (*Pfeiffer, Oberlin,* Ber. **57,** 208; **60,** 2142; *Pfeiffer, Oberlin, Konermann,* Ber. **58,** 1947; *Pfeiffer, Haack, Willems,* Ber. **61,** 294; *Pfeiffer, Angern, Haack, Willems,* Ber. **61,** 839, 1923; *Pfeiffer, Willems,* Ber. **62,** 1242; *Perkin, Rây, Robinson,* J. **1926,** 941; **1927,** 2094; **1928,** 1504).

Ceroxenes, containing a xanthene ring combined with an anthracene ring, are prepared either analogously to anthraquinone (Vol. III, p. 656) from fluorans with fuming sulfuric acid or from 1-phenoxyanthraquinone with concentrated sulfuric acid (*Decker,* Ann. **348,** 210; *Decker, v. Fellenberg,* Ann. **356,** 317):



Fluoran — Ceroxonol — 1-Phenoxyanthraquinone

An important derivative of ceroxonol is **cerulein**:

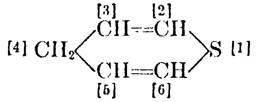


an olive-green cotton dye, fast to light; it is obtained by treating gallein with concentrated sulfuric acid. It is a derivative of anthraquinone.

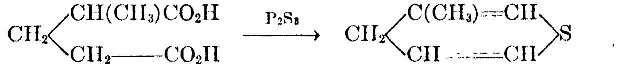
2. SIX-MEMBERED RINGS WITH ONE S-ATOM

1,4-Thiapyrans

Six-membered rings containing sulfur as a hetero atom occur in the derivatives (of which only a few are known) of the hypothetical 1,4-**thiapyran**, *penthiophene*:



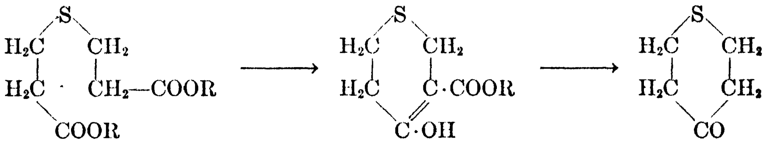
3-Methyl-1,4-thiapyran, oil, b.p. 134°, d^{19} 0.994, is formed from α-methylglutaric acid with P_2S_3, in the same way as thiophene is obtained from succinic acid (p. 24) (*Krekeler*, Ber. **19**, 3266):



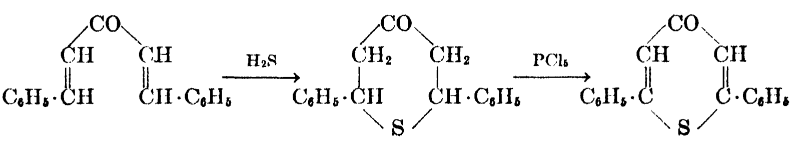
α-Methylglutaric acid — 3-Methyl-1,4-thiapyran

It gives the same color reactions as thiophene with isatin or phenanthraquinone and sulfuric acid. It is more unstable than the thiophenes, being oxidized even by very dilute potassium permanganate solution to acetic acid and oxalic acid. With acetyl chloride and $AlCl_3$ it gives **acetylmethyl-1,4-thiapyran,** $C_5H_4(CO\text{-}CH_3)(CH_3)S$, b.p. 235°.

1,4-Thiapyrone and **1,4-thiapyranone** are prepared: (*a*) From β-thiodipropionic acid esters by application of the Dieckmann reaction, which gives 4-hydroxy-5,6-dihydro-1,2-thiapyran-3-carboxylic acid ester, and hydrolysis of the latter to 1,4-thiapyranone (*Bennett, Scorah*, J. **1927**, 194):



(*b*) By the action of H_2S on diolefin ketones, such as dibenzalacetone, in the presence of sodium acetate and dehydrogenation of the thiapyranones so formed with PCl_5 (*Arndt, Nachtwey, Pusch*, Ber. **58**, 1633):



2,6-Diphenyl-1,4-thiapyranone

1,4-Thiapyranone, m.p. 66°, from **4-hydroxy-5,6-dihydro-1,2-thiapyran-3-carboxylic acid**, b.p. 150–151°.

2,6-Diphenyl-1,4-thiapyrone, m.p. 133°. **2,6-Diphenyl-1,4-thiapyranone** occurs in two stereoisomeric forms, m.p. 114° and 88°.

The products of the reaction of carbon disulfide and caustic alkali with ketones of the type RCH$_2$COCH$_2$R are derivatives of 1,4-thiapyrone (*Apitzsch*, Ber. **38**, 2888; *Apitzsch, Kelber*, Ber. **43**, 1259).

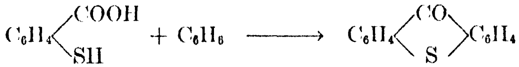
The **BENZOTHIAPYRANS** include the sulfur analogues of chromone, flavone, and flavanone. Literature: *v. Braun*, Ber. **43**, 3225 (thiochroman); *Simonis, Elias*, Ber. **49**, 768 (thiochromenes); *Ruhemann*, Ber. **46**, 2191, 3384 (thioflavones); *v. Auwers, Arndt*, Ber. **42**, 2706; *Arndt*, Ber. **56**, 1271 (thioflavanones).

For spectrochemical data, see the work of *F. Krollpfeiffer*, Ber. **56**, 1819; **58**, 1654, 1677.

The **DIBENZO DERIVATIVES** of 1,4-**THIAPYRAN** are the sulfur analogues of xanthenes and xanthones, the **thiaxanthenes** and **thiaxanthones**. They are prepared by the following methods:

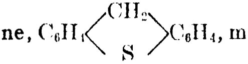
1. From phenylthiosalicylic acid with concentrated sulfuric acid or acetic anhydride.

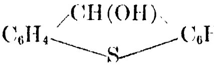
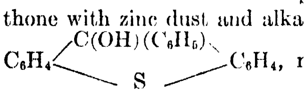
2. By condensation of thiosalicylic acid (Vol. III, p. 360) or dithiosalicylic acid with benzene hydrocarbons, halogen derivatives of benzenes, and phenols by means of concentrated H$_2$SO$_4$ (*Ullmann, v. Glenck*, Ber. **49**, 2487):

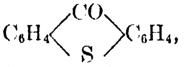
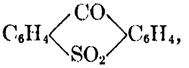


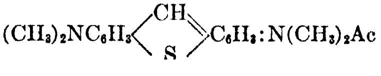
$$C_6H_4{<}\genfrac{}{}{0pt}{}{COOH}{SH} + C_6H_6 \longrightarrow C_6H_4{<}\genfrac{}{}{0pt}{}{CO}{S}{>}C_6H_4$$

3. Trihydroxythiaxanthones are obtained from gallic acid and thiophenols in the presence of concentrated H$_2$SO$_4$ (*Ullmann, Sone*, Ber. **44**, 2146).

Thiaxanthene,  $C_6H_4{<}\genfrac{}{}{0pt}{}{CH_2}{S}{>}C_6H_4$, m.p. 128°, b.p. 340°, is formed pyrogenically from phenyl tolyl sulfide and also by reduction of thiaxanthone with hydriodic acid and phosphorus.

Thiaxanthydrol,  $C_6H_4{<}\genfrac{}{}{0pt}{}{CH(OH)}{S}{>}C_6H_4$, m.p. 97°, by reduction of thiaxanthone with zinc dust and alkali (*Mayer*, Ber. **42**, 1135). **Phenylthiaxanthenol**,  $C_6H_4{<}\genfrac{}{}{0pt}{}{C(OH)(C_6H_5)}{S}{>}C_6H_4$, m.p. 106°, from thiaxanthone and C$_6$H$_5$MgBr (*Gomberg, Cone*, Ann. **376**, 201). Attempts to isolate the free phenylthiaxanthyl radical: *Gomberg, Minnis*, Am. **43**, 1940.

Thiaxanthone, *benzophenone sulfide*,  $C_6H_4{<}\genfrac{}{}{0pt}{}{CO}{S}{>}C_6H_4$, m.p. 207°, b.p. 273°, is isomeric with xanthione (p. 191); it is prepared from phenylthiosalicylic acid (*Graebe, Schultess*, Ann. **263**, 1) and from thiosalicylic acid and benzene by condensation in the presence of concentrated H$_2$SO$_4$. Oxidation converts it to "**benzophenone sulfone**,"  $C_6H_4{<}\genfrac{}{}{0pt}{}{CO}{SO_2}{>}C_6H_4$, m.p. 187°, which is also obtained by oxidation of the **diphenylmethane sulfone** CH$_2$(C$_6$H$_4$)$_2$SO$_2$, m.p. 170° (from diphenylmethane with chlorosulfonic acid) (*Lapworth*, J. **73**, 402), and from *o*-carboxydiphenyl sulfone with concentrated sulfuric acid [*Ullmann, Lehner*, Ber. **38**, 735; *Weedon, Doughty*, Am.Chem.J. **33** (1905), 386]. For *tetramethyldiaminodiphenylmethane sulfone* and *tetramethyldiaminobenzophenone sulfone*, see *Sachs*, Ber. **33**, 965. For other derivatives of thiaxanthone, see *Mayer*, Ber. **42**, 3046; **43**, 584; *Ullmann, v. Glenck*, Ber. **49**, 2487. **Thiopyronine**, the dyestuff corresponding to pyronine:



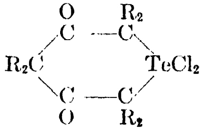
$$(CH_3)_2NC_6H_3{<}\genfrac{}{}{0pt}{}{CH}{S}{>}C_6H_3{:}N(CH_3)_2Ac$$

is prepared from tetramethyldiaminodiphenylmethane by treatment with a solution of sulfur in fuming sulfuric acid and yields on oxidation **tetramethyldiaminothiaxanthone,** $CO(C_6H_3N(CH_3)_2)_2S$, m.p. 288° (*Biehringer, Topaloff,* J.pr. **65,** 499).

SELENAXANTHONES are also known.

Selenaxanthone, m.p. 192°, from (chloroseleno)phenol-*o*-carboxylic acid chloride and benzene in the presence of aluminum chloride (*Lesser, Schoeller,* Ber. **47,** 2505; *Lesser, Weiss,* Ber. **57,** 1078).

TELLURAPYRANS. β-Diketones react with $TeCl_4$ to give cyclic tellurium compounds having the following constitution (*Morgan,* J. **127,** 2611):



3. SIX-MEMBERED RINGS WITH ONE N-ATOM

(a) Pyridines*

The pyridine ring, consisting of five methine groups and one nitrogen atom, is one of the most important heterocyclic systems. Pyridine is the parent compound of a number of natural products, including various alkaloids. It is present in the products of the pyrolysis of organic compounds containing nitrogen. Pyridine derivatives have been obtained from coal tar (*Meyer, Hofmann,* Mo. **37,** 681; *Eckert, Loria,* Mo. **38,** 225), shale tar [*Eguchi,* Bull.Chem.Soc.Japan **2** (1927), 176], wood tar, lignite tar (in small quantities), low-temperature tar (*Fromm, Eckard,* Ber. **56,** 948; *Morgan,* J.Soc.Chem.Ind. **47T,** 131) and bone oil (*cf.* pp. 203, 205). For the occurrence of pyridine in fusel oil, see *Bamberger, Einhorn,* Ber. **30,** 224.

The first pyridine bases were isolated from bone oil in 1846 by *Anderson,* who gave the parent substance the name of pyridine. The bases were thoroughly investigated from 1879 on by *Weidel* and his pupils, and by *Ladenburg.*

The formation of the pyridine bases in bone oil is due to the interaction of fats (glycerol esters) with compounds containing ammonia (such as proteins); the acrolein first formed reacts with the ammonia (*cf.* method of preparation *1*). Bone glue containing no fats yields not pyridine bases, but pyrroles (p. 29) (*Weidel, Ciamician,* Ber. **13,** 83). Coal tar is the principal source of technical pyridine bases.

The outstanding chemical property of the pyridine ring is its resistance to oxidation, in which it resembles the benzene ring. The same reagents which convert alkylbenzenes to benzoic acids produce pyridinecarboxylic acids from homologues of pyridine. This similarity in behavior to the aromatic series caused the postulation of a structural formula for pyridine analogous to that of benzene. The *Körner-Dewar* formula for pyridine (I), based mostly on intuition, is adapted from the benzene formula, with a CH-group replaced by a trivalent nitrogen. The experimental evidence for this structure was developed later (see p. 197):

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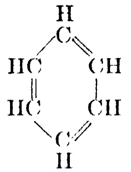
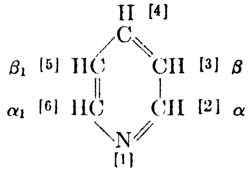
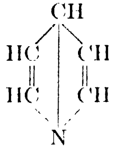
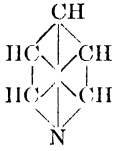
* For dyestuffs of the pyridine and quinoline group, see *Fierz-David:* Künstliche organische Farbstoffe (Springer, Berlin, 1926).


Benzene according to *Kekulé*

(I) 
Pyridine according to *Körner* (1869) and *Dewar* (1871)

While in the *Körner-Dewar* pyridine formula the nitrogen atom is bound to two carbon atoms, the so-called diagonal formula (II), proposed by *Riedel* on the basis of the relation of pyridine to acridine, shows the nitrogen atom connected to three different carbon atoms. To these two structures a third was added in 1891 by *Bamberger* and *von Pechmann* (Ber. 24, 3151); this is the centric pyridine formula (III), which corresponds to the *Claus-Armstrong* formula for benzene:

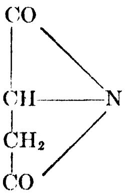
(II) 
Riedel

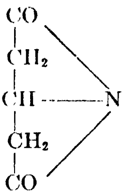
(III) 
Bamberger and *v. Pechmann*

To determine whether the N-atom in pyridine was bound to two or to three carbon atoms, *Kekulé*, from 1880 to 1890, undertook a series of experiments, whose results he reported on March 11, 1890, to a special meeting of Deutsche Chemische Gesellschaft called to celebrate the twenty-fifth anniversary of his theory of the structure of benzene. In 1929 *Kekulé's* treatise, "Über die Konstitution des Pyridins," was published for the first time in the biography "August Kekulé" by *Richard Anschütz* (Vol. II, p. 768).

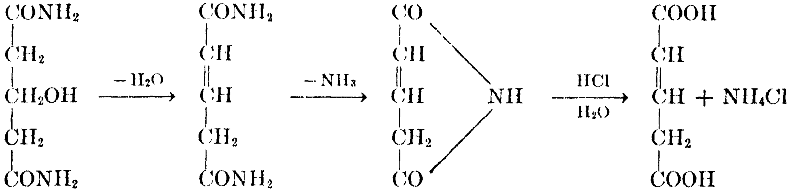
In the introduction of this important treatise *Kekulé* compared the pyridine ring to the benzene ring thus: "There are apparently two types of rings. Pyridine, like similar substances, is not really a ring, but a chain closed in a ring-shape by a lock. It appears as a ring, if the lock is treated as a member of the ring, but such a ring is always easier to open, and always at the lock, than a true ring containing equivalent members."

Proceeding on the assumption that the fumarimide (IV) prepared by heating the acid ammonium salt of malic acid, which is converted by hydrolysis to inactive aspartic acid, corresponds to formula II, *Kekulé* sought to prepare homofumarimide (V) by heating the ammonium salt of β-hydroxy glutaric acid, but without result.

(IV) 
Fumarimide

(V) 
The desired homofumarimide

Therefore *Kekulé* approached the problem in another way. In 1884 *Alfred Behrmann* and *A. W. v. Hofmann* had prepared citrazinic acid by the action of sulfuric acid on citramide; in 1887 *Ruhemann* recommended a diagonal formula for it. *Kekulé* treated the amide of β-hydroxy glutaric acid with sulfuric acid and obtained a compound which he first considered to be 2,6-pyridinediol, since it was converted to pyridine by distillation over zinc dust and to pentachloropyridine by phosphorus pentachloride. A more thorough investigation disclosed that this compound was not 2,6-pyridinediol, but glutaconimide, resulting from β-hydroxyglutaramide by elimination of water and ammonia, with intermediate formation of glutaconamide, which gives the imide when treated with sulfuric acid. When heated with hydrochloric acid the imide yields ammonium chloride and glutaconic acid.



β-Hydroxyglutaramide — Glutaconamide — Glutaconimide — Glutaconic acid

Since attempts to condense β-aminoglutaric acid and β-aminoglutaric acid monoethyl ester by heat or sulfuric acid or phosphorus pentachloride to cyclic derivatives in which the N-atom is bound to three carbon atoms failed, *Kekulé* concluded that "for the present the *Körner-Dewar* formula for pyridine should be preferred to the diagonal formula proposed by *Riedel*."

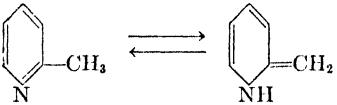
The centric formula III (*Bamberger* and *v. Pechmann*) of pyridine, in which the "*centric bonds*" are in labile equilibrium, provides an explanation for the many conversions without displacement of the double bonds, and therefore differentiates pyridine from other compounds such as glutaconic acid and glutaconimide which are closely related to it genetically.

The formation of pyridine from piperidine (pentamethylenimine) by dehydrogenation is significant in the determination of its constitution (see p. 200, No. *5*). Since piperidine is synthesized from trimethylene cyanide through the hydrochloride of pentamethylenediamine (see p. 220), it follows that pyridine also contains an unbroken chain of five carbon atoms.

Another important factor clarifying the constitution of pyridine is the oxidation of quinoline, whose constitution is certain, to pyridinedicarboxylic acid (quinolinic acid, p. 215), which can be decarboxylated to pyridine.

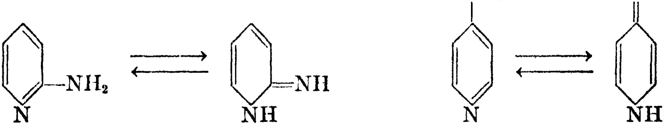
Tautomerism of the Pyridine Ring

A remarkable characteristic of the pyridine series is the wandering of hydrogen atoms in 2- and 4-substituted pyridines. The reactivity of the hydrogen atoms of the alkyl groups in 2- and 4-alkylpyridines has been recognized for a long time (see p. 204). More recent investigations have shown that 2- and 4-alkylpyridines can react in a tautomeric form, such as 2-methylenedihydropyridine (II), the so-called *pyridone methide* (*Tschitschibabin*, Ber. **61**, 547):



(I) (II)

This reactivity in two tautomeric forms is especially marked in the case of 2- and 4-aminopyridine, which sometimes react in the forms III and IV, and sometimes as imines, formulas IIIa and IVa (*Tschitschibabin*, Ber. **57**, 1168, 2092; **58**, 1704), and also in the case of the 2- and 4-hydroxypyridines (see below):



(III) **(IIIa)** **(IV)** **(IVa)**

This tautomerism does not appear in the 3-derivatives of pyridine. 3-Aminopyridine, *e.g.*, reacts only in the amine form; it behaves much like aniline. (*Cf.* the difference between the *m*-substituents and the *o*- and *p*-substituents in the benzene series.)

Methods of Synthesizing Pyridine Derivatives.—(*1*) When aldehyde ammonia compounds are heated alone or with aldehydes or ketones alkylpyridines are formed; homogeneous pyridine derivatives cannot be obtained by this method [*Tschitschibabin, Oparina*, J.Russ.Phys. Chem.Soc. **54** (1922), 420, 601]:

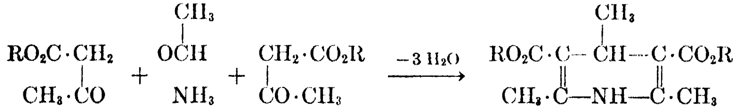
$$CH_3CHOH(NH_2) + 3\,CH_3CHO = C_5H_3(CH_3)(C_2H_5)N + 4\,H_2O$$

2-Methyl-3-ethylpyridine
(Aldehyde-collidine)

In this reaction apparently several aldehyde molecules join to form an unsaturated aldehyde with a longer carbon chain, which then condenses with ammonia to form a ring. 3-*Picoline* (p. 204) can be prepared by heating glycerol with P_2O_5 and substances containing ammonia, such as acetamide or, better, ammonium phosphate (*Schwarz*, Ber. **24**, 1676); homologous pyridines and pyrazines are formed as by-products.

(*2*) A very general method for the synthesis of pyridine derivatives, yielding definite products, consists in the condensation of *β-oxo carboxylic acid esters* and *β-diketones* with *aldehydes* and *ammonia* (*Hantzsch's* method):

Example (a): Acetoacetic ester (2 mols), acetaldehyde, and NH_3 (or aldehyde-ammonia) yield 2,4,6-*trimethyl*-1,4-*dihydrodinicotinic acid ester* (dihydrocollidinedicarboxylic acid ester), which can be readily converted into the corresponding pyridine derivative by elimination of two H-atoms (*Hantzsch*, Ann. **215**, 1; Ber. **18**, 2579):



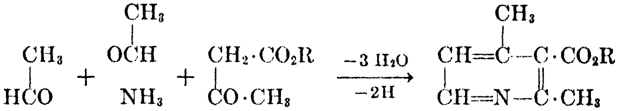
$$\begin{matrix} RO_2C\cdot CH_2 \\ | \\ CH_3\cdot CO \end{matrix} + \begin{matrix} CH_3 \\ | \\ OCH \\ NH_3 \end{matrix} + \begin{matrix} CH_2\cdot CO_2R \\ | \\ CO\cdot CH_3 \end{matrix} \xrightarrow{-3\,H_2O} \begin{matrix} & & CH_3 & & \\ & & | & & \\ RO_2C\cdot C & - & CH & - & C\cdot CO_2R \\ \| & & & & \| \\ CH_3\cdot C & - & NH & - & C\cdot CH_3 \end{matrix}$$

2,4,6-Trimethyl-1,4-dihydrodinicotinic acid ester

In place of acetaldehyde, formaldehyde or benzaldehyde (*Lachwicz*, Mo. **17**, 343), or chloroacetaldehyde (*Benary*, Ber. **51**, 567), can be used; the second mol of acetoacetic ester can be replaced by 1,3-diketones such as acetylacetone and benzoylacetone (*Beyer*, Ber. **24**, 1669).

In the above reactions the aldehyde and acetoacetic ester first condense to ethylidene-*bis*-acetoacetic ester, $CH_3CH(CH(COOR)COCH_3)_2$, a 1,5-diketone, which is closed to a pyridine ring by ammonia in the same way as 1,4-diketones are closed to pyrrole rings by ammonia (p. 15). When primary and secondary amines are used in place of ammonia, the reaction stops at the formation of alkylidene-*bis*-acetoacetic esters, so it is used for the preparation of the latter (*cf. Knoevenagel*, Ber. **31**, 738). The reaction is clarified by the fact that trimethyldihydrodinicotinic acid ester and similar compounds are also obtained in good yield by condensation of alkylideneacetoacetic esters and *β*-amino crotonic acid esters, the latter adding to the unsaturated bond of the former, forming a ring (*cf. Beyer*, Ber. **24**, 1667; *Knoevenagel, Fries*, Ber. **31**, 761; *Knoevenagel, Brunswig*, Ber. **35**, 2172; *Benary*, Ber. **44**, 489). Unsymmetrically substituted pyridine derivatives have also been prepared by this method.

Example (b): 2,4-Dimethylnicotinic acid ester is formed from acetoacetic ester (1 mol) and acetaldehyde (2 mols) with NH_3:

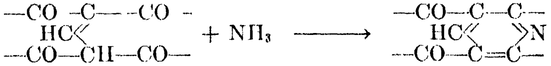


$$\begin{array}{c}\mathrm{CH_3}\\|\\\mathrm{HCO}\end{array} + \begin{array}{c}\mathrm{CH_3}\\|\\\mathrm{OCH}\\\mathrm{NH_3}\end{array} + \begin{array}{l}\mathrm{CH_2\cdot CO_2R}\\|\\\mathrm{CO\cdot CH_3}\end{array} \xrightarrow[-2H]{-3\,H_2O} \begin{array}{l}\qquad\mathrm{CH_3}\\\qquad|\\\mathrm{CH{=}C{-}C\cdot CO_2R}\\|\qquad\quad\|\\\mathrm{CH{=}N{-}C\cdot CH_3}\end{array}$$

2,4-Dimethylnicotinic acid ester

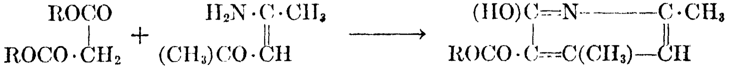
The mechanism of this reaction is similar to that of example (a); the dihydro derivative first produced is probably oxidized by excess aldehyde to the corresponding pyridine. This reaction can be varied by the use of different aldehydes.

In both these examples, dihydropyridine derivatives are the primary products. This intermediate step is eliminated and the pyridine derivatives are obtained immediately when hydroxymethyleneacetoacetic ester or hydroxymethyleneketones are condensed with β-amino crotonic acid ester (*Claisen*, Ber. **26**, 2734), or in general when NH_3 acts on the 1,5-diketones which result from the condensation of ethoxymethyleneacetoacetic ester and similar compounds with β-oxo carboxylic acid esters or 1,3-diketones (Ger. Pat. 79863, 1893; *Claisen*, Ann. **297**, 12; *Knoevenagel*, Ber. **36**, 2180; *Mumm*, *Bohme*, Ber. **54**, 726; *Benary*, *Psille*, Ber. **57**, 828; *Benary*, Ber. **60**, 914; *Späth*, *Burger*, Ber. **48**, 265; Ger. Pat. 418218, 1923, Frdl. **XV**, 1487):



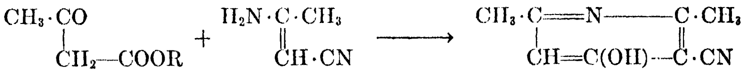
$$\begin{array}{l}\mathrm{-CO-C---CO-}\\\mathrm{HC\langle}\\\mathrm{-CO-CH-CO-}\end{array} + \mathrm{NH_3} \longrightarrow \begin{array}{l}\mathrm{-CO-C-C-}\\\mathrm{HC\langle\qquad\rangle N}\\\mathrm{-CO-C{=}C-}\end{array}$$

Malonic ester and β-amino crotonic acid ester give 2,4-dihydroxypicolinic acid ester; malonic ester and acetylacetoneimine give hydroxydimethylnicotinic acid ester (*Knoevenagel*, *Cremer*, Ber. **35**, 2390):



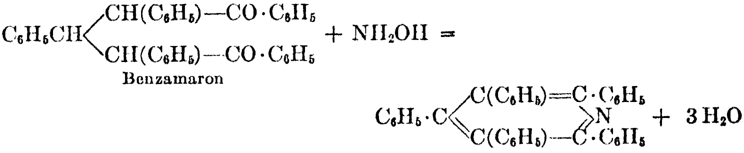
$$\begin{array}{r}\mathrm{ROCO}\\|\\\mathrm{ROCO\cdot CH_2}\end{array} + \begin{array}{l}\mathrm{H_2N\cdot C\cdot CH_3}\\\qquad\|\\\mathrm{(CH_3)CO\cdot CH}\end{array} \longrightarrow \begin{array}{l}\mathrm{(HO)C{=}N{-}{-}{-}C\cdot CH_3}\\\qquad|\qquad\qquad\|\\\mathrm{ROCO\cdot C{=}C(CH_3){-}CH}\end{array}$$

The formation of 4-hydroxypyridine derivatives by condensation of dinitriles (Vol. I) with β-oxo carboxylic acid esters by means of gaseous HCl also belongs in this group of reactions (*v. Meyer*, J.pr. **70**, 560):



$$\begin{array}{l}\mathrm{CH_3\cdot CO}\\|\\\mathrm{CH_2{-}COOR}\end{array} + \begin{array}{l}\mathrm{H_2N\cdot C\cdot CH_3}\\\qquad\|\\\mathrm{\quad CH\cdot CN}\end{array} \longrightarrow \begin{array}{l}\mathrm{CH_3\cdot C{=}N{-}{-}{-}C\cdot CH_3}\\\qquad|\qquad\qquad\|\\\mathrm{CH{=}C(OH){-}C\cdot CN}\end{array}$$

(*3*) 1,5-Diketones, especially those in which phenyl radicals are attached to the keto groups (1,3-dibenzoylparaffins), are converted to pyridines by treatment with hydroxylamine (*Knoevenagel*, Ann. **281**, 36; **303**, 225; *Blaise*, *Montagne*, C.r. **180**, 1760):

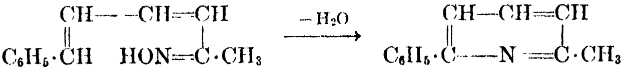


$$\mathrm{C_6H_5CH}\begin{array}{l}\mathrm{\diagup CH(C_6H_5){-}CO\cdot C_6H_5}\\\mathrm{\diagdown CH(C_6H_5){-}CO\cdot C_6H_5}\end{array} + \mathrm{NH_2OH} = \mathrm{C_6H_5\cdot C}\begin{array}{l}\mathrm{\diagup C(C_6H_5){=}C\cdot C_6H_5}\\\qquad\qquad\qquad\mathrm{\rangle N}\\\mathrm{\diagdown C(C_6H_5){-}C\cdot C_6H_5}\end{array} + 3\,\mathrm{H_2O}$$

Benzamaron

Pentaphenylpyridine

Several oximes of diolefin monoketones yield pyridines when dry-distilled (*Scholtz*, Ber. **28**, 1726; **29**, 613; **32**, 1935; *Scholtz*, *Meyer*, Ber. **43**, 1861):

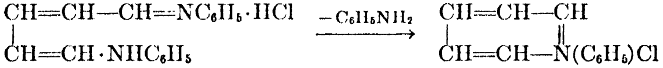


$$\begin{array}{l}\mathrm{\quad CH{-}{-}CH{=}CH}\\\quad\|\qquad\qquad\quad|\\\mathrm{C_6H_5\cdot CH\quad HON{=}C\cdot CH_3}\end{array} \xrightarrow{-H_2O} \begin{array}{l}\mathrm{\quad CH{-}CH{=}CH}\\\quad\|\qquad\qquad|\\\mathrm{C_6H_5\cdot C{-}{-}N{=}C\cdot CH_3}\end{array}$$

Cinnamylideneacetone oxime 2-Phenyl-6-methylpyridine

The same 2-phenyl-6-tolylpyridine is obtained from $C_6H_5CH{:}CH\cdot CH{:}CH\cdot C(NOH)C_6H_4CH_3$ and $CH_3C_6H_4CH{:}CH\cdot CH{:}CH\cdot C(NOH)C_6H_5$, a proof of the identity of the 2- and the 6-positions and for the symmetrical structure of pyridine (*Scholtz, Wiedemann*, Ber. **36**, 845).

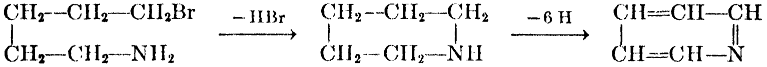
(*4*) When the arylamine derivatives of glutaconaldehyde are boiled with hydrochloric acid, or when their hydrochlorides are heated, 1 mol of arylamine is eliminated and N-arylpyridinium chlorides are formed (see p. 201 and *Zincke*, Ann. **333**, 328; *Dieckmann*, Ber. **38**, 1650; *Dieckmann, Beck*, Ber. **38**, 4122):



$$\begin{array}{l} CH{=}CH{-}CH{=}NC_6H_5\cdot HCl \\ | \\ CH{=}CH\cdot NHC_6H_5 \end{array} \xrightarrow{-C_6H_5NH_2} \begin{array}{l} CH{=}CH{-}CH \\ |\qquad\qquad\quad \| \\ CH{=}CH{-}N(C_6H_5)Cl \end{array}$$

Cf. the formation of 3-chloropyridine from α-chloroglutaconaldehyde and NH_3 (*Dieckmann*, Ber. **38**, 1651; *Baumgarten*, Ber. **58**, 2018).

(*5*) Pyridines are prepared by oxidation of the synthetic hexahydropyridines, piperidines or pentamethylenimines (p. 220) with H_2SO_4 or silver acetate (*Tafel*, Ber. **25**, 1621):



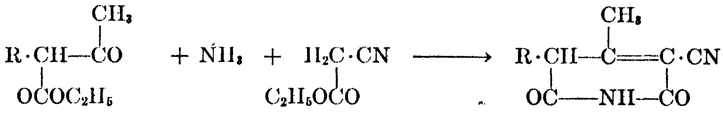
$$\begin{array}{l} CH_2{-}CH_2{-}CH_2Br \\ | \\ CH_2{-}CH_2{-}NH_2 \end{array} \xrightarrow{-HBr} \begin{array}{l} CH_2{-}CH_2{-}CH_2 \\ |\qquad\qquad\quad | \\ CH_2{-}CH_2{-}NH \end{array} \xrightarrow{-6\,H} \begin{array}{l} CH{=}CH{-}CH \\ |\qquad\qquad \| \\ CH{=}CH{-}N \end{array}$$

5-Bromoamylamine Piperidine Pyridine

(*6*) Hydroxypyridine derivatives (pyridones) are obtained from pyrone derivatives (p. 177) with ammonia, the oxygen atom in the pyrone ring being replaced by the NH-group. All simple pyrylium salts are similarly converted by ammonia to pyridines even without heat (*Dilthey*, J.pr. **102**, 209).

(*7*) 2,6-Pyridinediol derivatives, which can be considered as imides of glutaconic acid and its homologues, are prepared from glutaconamic acid and similar compounds by ring-closure. Citrazinic acid (dihydroxypyridinecarboxylic acid) is formed from aconitic acid ester with NH_3, and from citramide.

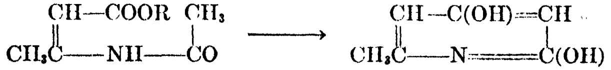
(*8*) Derivatives of 2,6-pyridinediol can also be synthesized by condensation of acetoacetic esters and cyanoacetic ester with ammonia or primary amines, or by condensation of benzaldehyde (1 mol), NH_3, and cyanoacetic ester (2 mols) (*Guareschi*, C. **1897, I**, 927; **1899, II**, 118; **1905, II**, 681):



$$\begin{array}{l} \qquad\quad CH_3 \\ \qquad\quad | \\ R\cdot CH{-}CO \\ \quad | \\ OCOC_2H_5 \end{array} + NH_3 + \begin{array}{l} H_2C\cdot CN \\ \quad | \\ C_2H_5OCO \end{array} \longrightarrow \begin{array}{l} \qquad\qquad CH_3 \\ \qquad\qquad | \\ R\cdot CH{-}C{=}C\cdot CN \\ \qquad | \qquad\qquad | \\ \qquad OC{-}NH{-}CO \end{array}$$

2(1)-Pyridones result from similar condensations of 1,3-diketones and ammonia or of β-aminoketones, such as diacetonamine, $CH_3COCH_2C(CH_3)_2NH_2$, or acetylacetoneimine, $CH_3CO\cdot CH{:}C(CH_3)NH_2$, with cyanoacetic ester (*Guareschi*, C. **1893, II**, 648; *Issoglio*, C. **1905, II**, 336); they are also formed by condensation of β-aminocrotonic acid esters with alkylidenemalonic esters (*cf. Knoevenagel, Fries*, Ber. **31**, 761).

(*9*) The action of sodium alcoholate on β-acetamidocarboxylic acid esters produces 2,6-pyridinediols (Ger. Pat. 102894, 1898):



$$\begin{array}{l} \quad CH{-}COOR\;\; CH_3 \\ \quad \| \qquad\qquad\quad | \\ CH_3C{-}NH{-}CO \end{array} \longrightarrow \begin{array}{l} \quad CH{-}C(OH){=}CH \\ \quad \| \qquad\qquad\qquad | \\ CH_3C{-}N{=}C(OH) \end{array}$$

β-Acetamidocrotonic acid ester **6-Methyl-2,4-pyridinediol**

(10) A synthesis of theoretical interest is the formation of 3-chloro- or 3-bromopyridine from pyrrole by heating with $CHCl_3$ or $CHBr_3$ and $NaOC_2H_5$ (p. 30). With CH_2I_2 pyridine is obtained, and with $C_6H_5CHCl_2$, 3-phenylpyridine (*Ciamician, Silber,* Ber. **20,** 191).

(11) When the vapors of N- or 2-alkylpyrroles are passed through a slightly incandescent tube, or when the compounds themselves are heated with hydrochloric acid, pyridine derivatives are formed; 1- and 2-methylpyrrole give pyridine and 1-benzylpyrrole yields 3-phenylpyridine (p. 31 and *Dennstedt, Zimmermann,* Ber. **19,** 2196; *Pictet,* Ber. **38,** 1946). Small amounts of pyridine result from the action of acetylene on hydrocyanic acid at 800–950° (*Meyer, Tanzen,* Ber. **46,** 3184, 3195; *Meyer, Wesche,* Ber. **50,** 424, 435). Mixtures of pyridine bases are obtained from ammonia and acetylene at 300° and in the presence of contact catalysts (alumina, ferric oxide) [*Tschitschibabin,* J.Russ.Phys.Chem.Soc. **47** (1916), 703; *Tschitschibabin, Oparina, ibid.* **54** (1924), 601].

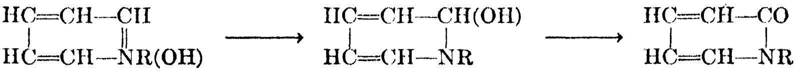
(12) Another synthesis of theoretical interest is the conversion of benzene and its homologues into pyridine when a dilute benzene solution of sulfuryl azide (*Curtius, Schmidt,* Ber. **55,** 1571; *Schmidt,* Ber. **55,** 1581; **58,** 2409) or carbonyl azide (*Curtius, Bertho,* Sitz.-ber.Heidelberg. Akad.Wiss. **1924,** 3; **1925,** 3) is heated to 140°.

Behavior.—The pyridine bases are colorless liquids with a characteristic odor. Pyridine is miscible with water; the solubility of the homologues decreases rapidly and is usually greater in cold than in warm water.

1. Salts. The platinum double salt of the formula $(C_5H_5N \cdot HCl)_2PtCl_4$ loses 2 HCl when boiled for a long time with hydrochloric acid, forming $(C_5H_5N)_2PtCl_4$ (*cf.* pyrazoles, p. 92). The pyridines form addition compounds with many inorganic salts; those with $CdCl_2$, $HgCl_2$, and $AuCl_3$ are characteristic and serve for the separation of a mixture of bases [*Ladenburg,* Ann. **247,** 1; *cf. Varet,* C.r. **124,** 1155; *Pincussohn,* Z.anorg.Chem. **14** (1897), 379].

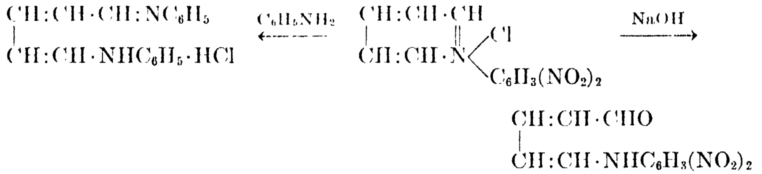
2. Pyridines combine with alkyl iodides to form *alkylpyridinium iodides.* The reaction is often violent. The pyridines also add chloroacetic acid and its homologues to give *pyridinebetaines* (*Kirpal,* Mo. **31,** 969). They also combine with dimethyl sulfate, acid chlorides, cyanogen bromide, 2,4-dinitrochlorobenzene, and similar compounds. Substituents in the 2,6-position sometimes slow down the formation of pyridinium salts, sometimes prevent it altogether (*cf. Meyer,* Mo. **25,** 1196).

When the alkylpyridinium iodides are treated with aqueous sodium hydroxide, the strongly basic pyridinium hydroxides first formed rearrange to the isomeric 2-hydroxydihydropyridines, which are rather unstable; the latter can be oxidized by potassium ferricyanide to 1-alkyl-2-pyridones (*Decker, Kaufmann,* J.pr. **84,** 219):



$$\begin{array}{l}HC{=}CH{-}CH\\ |\qquad\qquad\ \|\\ HC{=}CH{-}NR(OH)\end{array}\longrightarrow\begin{array}{l}HC{=}CH{-}CH(OH)\\ |\qquad\qquad\ |\\ HC{=}CH{-}NR\end{array}\longrightarrow\begin{array}{l}HC{=}CH{-}CO\\ |\qquad\qquad\ |\\ HC{=}CH{-}NR\end{array}$$

The dinitrophenylpyridinium chloride obtained from pyridine and 2,4-dinitrochlorobenzene is converted by treatment with alkali or various primary and secondary amines to highly colored derivatives of glutaconaldehyde or its tautomeric form (*Zincke*, Ann. **330**, 361; *Zincke*, *Würker*, Ann. **341**, 365; *Zincke*, *Weispfenning*, J.pr. **82**, 1):



The addition products of pyridine with cyanogen bromide, diphenyloxalimide chloride, PCl_5 (*König*, J.pr. **69**, 105; **70**, 19; *König*, *Bayer*, J.pr. **83**, 325; *Reitzenstein*, *Breuning*, J.pr. **83**, 97) and chlorosulfonic acid esters (*Baumgarten*, Ber. **57**, 1622) behave similarly. *Cf.* the synthesis of pyridine from derivatives of glutaconaldehyde (p. 200) which is the reverse of this decomposition.

Another conversion of the pyridine ring to glutaconaldehyde, developed by *Bucherer* (*Bucherer*, *Schenkel*, Ber. **41**, 1346; *Schenkel*, Ber. **43**, 2597; *Reitzenstein*, *Breuning*, Ber. **43**, 2939), occurs when the addition product of pyridine and 3 mols of sodium bisulfite, $C_5H_8N(O\cdot SO_2Na)_3 + 2\,H_2O$, is treated with aqueous sodium hydroxide.

For the products resulting from the action of alkali on the alkyl iodide addition products of 2- and 4-alkylpyridines, the pyridoneimides, see p. 197.

3. When alkylpyridinium iodides are heated to 300° the *alkyl groups shift* from the nitrogen atom to the 2- or 4-carbon atom, producing alkylpyridines (*Ladenburg*, Ber. **17, 772**); this is analogous to the formation of homologous anilines from N-alkylanilines (Vol. III, p. 78).

4. Methyl groups in the 2-position and, to a lesser extent, those in the 4-position undergo aldol condensations with aldehydes such as formaldehyde, chloral, and benzaldehyde; the *alkines* which are so formed often split off water, giving *stilbazoles* (*Bach*, Ber. **34, 2223**). Phthalic anhydride and imide react like the aldehydes (*Scholze*, Ber. **38, 2806**). 2-Picoline does not react with nitrosodimethylaniline, but does with its methyl iodide (*Kaufmann*, *Vallette*, Ber. **45, 1737, 1742**; *Fuchs*, *Grauaug*, Ber. **61**, 57). Methyl groups in the 3-position do not condense in this manner.

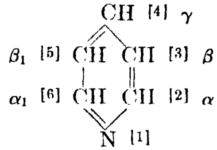
5. Oxidizing agents such as nitric acid and chromic acid do not, as a rule, attack pyridines. Alkylated and arylated pyridines are oxidized by $KMnO_4$ to pyridinecarboxylic acids or to open-chain compounds (*Delépine*, C.r. **184**, 206; *Tschitschibabin*, Ber. **37**, 1373).

6. Reducing agents such as sodium and alcohol or catalytic hydrogenation convert the pyridine bases to *hexahydropyridines* or piperidines, which can be split by various means to aliphatic compounds (*cf.* p. 221). When heated with hydriodic acid the pyridines are reduced to *paraffins*, pyridine giving pentane.

7. *Halogeno*, *nitro*, and *sulfonic acid* derivatives are prepared with far more difficulty from the pyridines than from the benzenes.

8. The amino group is introduced directly into pyridine by the action of sodium amide. For details, see the section on aminopyridines (pp. 207 *ff.*).

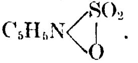
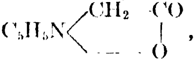
Isomers.—The positions of substituents in the pyridine ring are indicated by these symbols:



There are three possible monosubstituted products and six possible disubstituted products, all of which have been prepared in many cases. The position of alkyl groups in pyridines is determined by conversion into the corresponding pyridinecarboxylic acids, which have characteristic melting points, copper salts and esters. The pyridinecarboxylic acids are the keystones in the clarification of the constitution of pyridine derivatives, and the determination of their constitution is therefore especially important (p. 213).

PYRIDINE, C_5H_5N, m.p. −42°, b.p. 115.3°, d_4^{25} 0.9776 (*Heap, Jones, Speakman*, Am. **43,** 1936), is obtained from bone oil and coal tar, and is formed from all pyridinecarboxylic acids by distillation with lime. For several methods of preparing pyridine, see p. 201, Nos. *10, 11, 12.* It is a very weak base and does not color litmus. Its deliquescent *hydrochloride* $C_5H_5N \cdot HCl$ forms with $PtCl_4$ a sparingly soluble platinum double salt, $PtCl_4(C_5H_5N \cdot HCl)_2$, m.p. 264°. *Hydrobromide*, m.p. 206° (*Ruggli, Bolliger*, Helv. **4,** 633). The *perchlorate* is suitable for the separation of pure pyridine from mixtures with other pyridine bases (Ger. Pat. 451956, 1925, Frdl. **XVI,** 530) and for the microchemical determination (*Cordier*, Mo. **43,** 525). Pyridine mercuric chloride, $C_5H_5N \cdot HCl \cdot 2\,HgCl_2$, m.p. 178°; zinc chloride double salt, $2\,C_5H_5N \cdot ZnCl_2$, sparingly soluble in alcohol; *picrate*, m.p. 164°; *methyl iodide addition product*, m.p. 117°. For the numerous complex compounds with pyridine, see *P. Pfeiffer*, Organische Molekülverbindungen, Stuttgart, 1927.

Industrially, a mixture of pyridine bases is used for the denaturing of alcohol [Chem.Z. **37** (1913), 1035]. In the laboratory it is an indispensable solvent. Absolute pyridine (prepared with BaO) is used as the solvent in the determination of active hydrogen atoms by the method of *Zerewitinoff* (see Vol. I, p. 11), in the introduction of benzoyl groups into organic compounds by means of benzoyl chloride and in the ebullioscopic determination of molecular weights (K = 29.5 for 100 g. solvent).

Phosgene unites with 2 molar proportions of pyridine to give pyridinecarbonyl chloride, $[C_5H_5N(Cl)]_2CO$ (Ger. Pat. 109933, 1898). The addition products of pyridine with acid chlorides have been extensively investigated (for the addition products with acetyl chloride and oxalyl chloride see *Freudenberg, Peters*, Ber. **52,** 1463). The product from pyridine and benzoyl chloride has practical significance since it makes possible the introduction of the benzoyl group into alcohols, phenols, amines, β-diketones, and β-oxo carboxylic acids under mild conditions. The action of SO_2Cl_2 on pyridine is similar (*Baumgarten*, Ber. **60,** 1174); the addition product first formed yields **N-pyridiniumsulfonic acid,**  $C_5H_5N{<}\begin{matrix}SO_2\\ |\\ O\end{matrix}$. **Pyridinebetaine,**  $C_5H_5N{<}\begin{matrix}CH_2 - CO\\ \qquad |\\ \qquad O\end{matrix}$, m.p. 150° (dec.), is formed from pyridine and chloroacetic acid (*Kruger*, Ber. **23,** 2609). For the addition products of pyridine with dinitrochlorobenzene, cyanogen bromide, and the like, and their decomposition into glutaconaldehyde derivatives, see p. **202**. The red coloration produced when chloroformic acid ester is added to pyridine can be used to detect small quantities of pyridine (*Hopkins*, J. **117,** 278). For the addition product of sodium bisulfite to pyridine, see p. **202**.

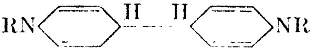
Bromine adds to pyridine hydrochloride to give a perbromide, which is useful in the bromination of organic compounds (*Rosenmund, Kuhnhenn*, Ber. **56**, 1262; *Rosenmund, Kuhnhenn, Lesch*, Ber. **56**, 2042).

Pyridine is readily converted by perbenzoic acid to *pyridine N-oxide*, m.p. 68°. Hydrochloride, m.p. 180°; picrate, m.p. 179° (*Meisenheimer*, Ber. **59**, 1848).

Pyridine is reduced by sodium and alcohol to piperidine. Piperidine hydrochloride is obtained by catalytic reduction of pyridine hydrochloride with a platinum oxide catalyst (*Hamilton, Adams*, Am. **50**, 2260).

With finely divided Na or K absolute pyridine forms an addition compound which contains 2 mols of base to 1 mol of alkali metal (*Emmert*, Ber. **47**, 2600; **49**, 1061); these compounds are converted by water to tetrahydro-2,2′- or 4,4′-bipyridine (see below, and *Emmert*, Ber. **50**, 31).

Derivatives of 4,4′-bipyridine are also produced by the reduction of pyridine with zinc dust and acetic anhydride (*Dimroth, Heene*, Ber. **54**, 2934). The citron yellow 1,1′-diacetyl-1,1′,4,4′-tetrahydro-4,4′-bipyridine, m.p. 125° (I), is prepared in this way.

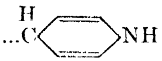


(I) R = $CO{\cdot}CH_3$
(II) R = H
(III) R = Alkyl

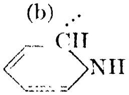
A similar product is formed when the pyridine-Na compound described above is treated with water (II). 1,1′-Dialkyltetrahydro-4,4′-bipyridines (III) are obtained by reduction of alkylpyridinium compounds with sodium amalgam (*Emmert*, Ber. **52**, 1351) or by electrolysis (*Emmert*, Ber. **42**, 1997).

The tetrahydro-1,4′-bipyridines dissociate into free radicals when warmed (*Emmert*, **53**, 370; *Dimroth, Heene*, Ber. **54**, 2934). The constitution of these radicals is not certain; they could be carbon radicals (formulas a and b) or derivatives of tetravalent nitrogen (c) (*Weitz, Nelken*, Ann. **425**, 187):

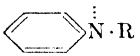
(a)



(b)



(c)



N-Benzoylpyridinium, m.p. 229°, dark brown, metallic platelets (*Weitz, Roth, Nelken*, Ann. **425**, 161); **N-benzylpyridinium**, brown-red, almost black crystals which give a very blue solution in alcohol (*Weitz, Nelken*, Ann. **425**, 187).

1. **HOMOLOGOUS PYRIDINES.** **Methylpyridines, picolines** (from pix = tar, since they were obtained from bone tar): **2-picoline**, b.p. 130°, d^{25} 0.940 gives *picolinic acid* on oxidation; **3-picoline**, b.p., 143°, d^{25} 0.9515, $HgCl_2$-salt: m.p. 145°, is produced by distillation of strychnine (see alkaloids) (*Ladenburg*, Ber. **23**, 3555), by heating glycerol with ammonium phosphate (p. 198), and by heating trimethylenediamine hydrochloride (*Ladenburg, Sieber*, Ber. **23**, 2730); it oxidizes to *nicotinic acid*. For the recovery of 2- and 3-picoline from coal tar see *Heap, Jones, Speakman*, Am. **43**, 1936. **4-Picoline**, b.p. 144°, d^{15} 0.957 (*Meisenheimer*, Ann. **420**, 197), is formed together with 2-methylpyridine in small amounts when pyridine methyl iodide (p. 203) is heated; it gives *isonicotinic acid* on oxidation.

Dimethylpyridines, lutidines (so named because of their isomerism with toluidines): **2,6-lutidine**, b.p. 142°, d 0.942; **2,4-lutidine**, b.p. 157°, d 0.949; and **3,4-lutidine**, b.p. 164°, are found in bone oil (*Mohler*, Ber. **21**, 1006; *Ahrens*, Ber. **29**, 2996); the latter also occurs in Scottish shale oil [*Garrett, Smythe*, Proc. Chem.Soc. **19** (1903), 164]. **3,5-Lutidine**, b.p. 170°, is prepared from its carboxylic acid (*Dürkopf, Göttsch*, Ber. **23**, 1113) and occurs in coal tar, together with **2,5-lutidine**, b.p. 160° (*Ahrens, Gorkow*, Ber. **37**, 2062).

2-Ethylpyridine, b.p. 148°, d 0.949, and **4-ethylpyridine**, b.p. 165°, d 0.952, are prepared by heating the ethyl iodide addition product of pyridine; the former is also formed by reduction of 2-pyridineëthanol (p. 212). **3-Ethylpyridine**, b.p. 166°, is formed together with 4-ethylpyridine by distillation of cinchonine or brucine (see alkaloids) with KOH or from 5-ethylpicolinic acid (*Koenigs, Hoffmann*, Ber. **58**, 191).

2,4,6-Trimethylpyridine, s-collidine, b.p. 172°, is prepared from the synthetic dihydrocollidinedicarboxylic acid ester (p. 198) by oxidation, saponification and decarboxylation; it is found in Scottish shale oil [*Garrett*, *Smythe*, Proc.Chem.Soc. **19** (1903), 164] and in coal tar (*Eckert*, *Loria*, Mo. **38**, 225). 2,4,5-**Collidine**, b.p. 165 to 168°, from coal tar (*Ahrens*, Ber. **29**, 2998). 2,3,4-**Collidine**, b.p. 185 to 188° (*Eckert*, *Loria*, Mo. **38**, 243), oxidizes to carbocinchomeronic acid. 2,3,6-**Trimethylpyridine**, b.p. 174° (734 mm.), from coal tar (*Eckert*, *Loria*, Mo. **38**, 225). 5-**Ethyl-2-methylpyridine**, *aldehydecollidine*, b.p. 178°, is obtained from several aldehyde compounds (p. 198). 6-**Ethyl-2-methylpyridine**, b.p. 160°, from 2-methylpyridine-6-ethanol by reduction (*Löffler*, *Thiel*, Ber. **42**, 137). 3-**Ethyl-4-methylpyridine**, *β-collidine*, b.p. 190 to 200°, from cinchonine by distillation with KOH, together with 3-ethylpyridine (*Koenigs*, Ber. **35**, 1351). Synthesis: *Ruzicka*, *Fornaser*, Helv. **2**, 338.

2-**Propylpyridine**, **conyrine**, b.p. 167°, is obtained from coniine (see alkaloids) by distillation with zinc dust. 2-**Isopropylpyridine**, b.p. 158°, is produced together with the 4-isomer (b.p. 178°) when the propyl or isopropyl iodide addition product of pyridine is heated; it is also prepared by reduction of 2-(*β*,*β*′-dihydroxyisopropyl)pyridine (p. **212**). 4-*t*-**Butylpyridine**, $C_5H_4N \cdot C(CH_3)_3$, b.p. 196–197°, is obtained similarly from 4-(*β*,*β*′,*β*″-trihydroxy-*t*-butyl)pyridine (p. **212**).

Parvoline, 2,3,4,5-**tetramethylpyridine**, b.p. 227–230°, from coal tar (*Ahrens*, Ber. **28**, 796).

2- and 4-**Benzylpyridine**, b.p. 276° and 287°, from 1-benzylpyridinium chloride or iodide at 270°, together with a small amount of 3-**benzylpyridine**, m.p. 34°, b.p. 287°, which is more advantageously prepared from 3-benzoylpyridine (p. 213) by reduction with hydriodic acid and phosphorus (*Tschitschibabin*, Ber. **36**, 2711). 1-Methyl-2- and 4-benzylpyridinium iodides are converted by aqueous sodium hydroxide, not to dihydropyridols (p. **201**), but by elimination of H_2O to 2- and 4-**benzylidene-1-methyldihydropyridine**, $(C_6H_5CH:)C_5H_4NCH_3$, which regenerate the pyridinium salts when treated with acids (*Decker*, *Wislocki*, Ber. **38**, 2496). See also the section on pyridone methides, p. **210**.

3,5-**Dibenzylpyridine**, m.p. 89°, is formed by condensation of benzaldehyde with benzoylpiperidine (p. **222**) (*Rügheimer*, Ann. **280**, 36).

2-**Phenylpyridine**, b.p. 269°, is prepared from its carboxylic acid, a decomposition product of benzo[*h*]quinoline, by decarboxylation (*cf.* p. **247**) and from 6-phenyl-2(1)-pyridone (p. **209**) by distillation with zinc dust (*Leben*, Ber. **29**, 1678). 3-**Phenylpyridine**, b.p. 270°, is obtained by decarboxylation of its carboxylic acid, a decomposition product of benzo[*f*]quinoline, by distillation of 1-benzylpyrrole through a slightly incandescent tube and by treatment of pyrrole with benzal chloride and sodium ethylate (p. 30). *p*-**Nitrophenylpyridine**, m.p. 117°, from nitroisodiazobenzene and pyridine, reduces to *p*-**aminophenylpyridine**, m.p. 102°, which yields 2-phenylpyridine when deaminated (*Kühling*, Ber. **29**, 167). 4-**Phenylpyridine**, m.p. 77°, b.p. 274°, by oxidation of the condensation product of acetoacetic ester with benzaldehyde and ammonia (*cf.* p. 198). A mixture of 2- and 4-phenylpyridine results from the action of benzenediazonium salts on pyridine (*cf.* *Tschitschibabin*, Ber. **37**, 1370).

6-**Phenyl-2-picoline**, b.p. 281°, from cinnamylideneacetone oxime (p. 199 and *Scholtz*, Ber. **28**, 1727). 2,6-**Diphenylpyridine**, m.p. 82°, is obtained: (*1*) by distillation of the oxime of cinnamylideneacetophenone (*cf.* method *3*, p. 199); (*2*) from 2,6-diphenyl-4-pyridinecarboxylic acid, prepared by heating diphenacylmalonic acid with ammonia; and (*3*) by oxidation of 2-phenyl-5,6-benzocinchoninic acid (*Paal*, Ber. **29**, 798; *Paal*, *Demeler*, Ber. **30**, 1499). 2,4,6-**Triphenylpyridine**, m.p. 137°; 2,3,5,6- and 2,3,4,6-**tetraphenylpyridine**, m.p. 179° and 233°, and **pentaphenylpyridine**, m.p. 240°, are produced by the action of hydroxylamine on benzaldiacetophenone, 1,3-dibenzoyldiphenylpropane, desoxybenzoinbenzylideneacetophenone and benzamaron (*cf.* p. 199, method *3*, and *Wislicenus*, Ann. **302**, 233, 240; *Knoevenagel*, Ann. **303**, 225). For the preparation (from the corresponding pyrylium compounds with NH_3) and properties of a large number of aryl-substituted pyridines, see *Dilthey*, J.pr. **102**, 209–240.

2,2′-**Bipyridine**, m.p. 69° (picrate, m.p. 158°), is formed when dried pyridine is heated with sublimed ferric chloride to 300° (*Hein*, *Retter*, Ber. **61**, 1790); it is also produced by distillation of copper picolinate (*Blau*, Mo. **10**, 375) and pyrogenically from pyridine (*Meyer*, *Hofmann-Meyer*, J.pr. **102**, 287) and 2-bromopyridine (*Wibaut*, *Overhoff*, Rec. **47**, 761); it forms a characteristic deep red ferrous complex salt. 3,3′-**Bipyridine**, m.p. 68°, b.p. 287°, from its dicarboxylic acid, an oxidation product of phenanthroline (p. 265). **4,4′-Bipyridine**, m.p. 112° (dried over H_2SO_4), b.p. 305°, is prepared together with an oily polymer of pyridine, $(C_5H_5N)_x$, by the action of sodium on pyridine (*Ahrens*, Ber. **24**, 1478; *Emmert*, Ber. **50**, 31). A **tetramethylbipyridine**, $[C_5H_2(CH_3)_2N]_2$, m.p. 149°, is obtained when 2,6-lutidine is heated; it oxidizes to a bipyridinetetracarboxylic acid, which gives 4,4′-bipyridine when decarboxylated (*Huth*, Ber. **32**, 2209). For derivatives of tetrahydro-4,4′-bipyridine, see pp. 204, 218.

For pyridylpyrrole see p. 31 and *Wibaut*, Rec. **45**, 657.

Vinylpyridine, b.p. 160°, is prepared from pyridineëthanol (p. 212) by elimination of water, from β-bromo-2-pyridinepropionic acid by elimination of CO_2 and HBr and from pyridine vapors and ethylene by passage through an incandescent tube (*Ladenburg*, Ber. **20**, 1644; *Einhorn*, Ann. **265**, 229).

2-Propenylpyridine, $(C_5H_4N)CH:CHCH_3$, b.p. 290°, can be prepared by the reaction of 2-picoline with paraldehyde at 260° (*Ladenburg*, Ann. **247**, 26); sodium and alcohol reduce it to propylpiperidine or inactive *coniine* (p. 332). **4-Propenylpyridine**, b.p. 201°, from 4-picoline and paraldehyde (*Ahrens*, Ber. **38**, 157). **2-Styrylpyridine**, *stilbazole*, $C_5(CH:CHC_6H_5)H_4N$, m.p. 61°, b.p. 325° by heating 2-picoline with benzaldehyde and $ZnCl_2$. Benzaldehyde and its substitution products react similarly with other 2-methylated pyridines, such as 6-phenyl-2-picoline and 2,4-lutidine; 2,6-lutidine gives 2,6-distyrylpyridine, $ArCH:CH(C_5H_3N)CH:CHAr$ (*Dehnel*, Ber. **33**, 3494; *Feist*, Ber. **34**, 464; *Backe*, Ber. **34**, 1893; *Duerig*, Ber. **35**, 2774; *Knick*, Ber. **35**, 2790; *Shaw*, J. **125**, 2363). **4-Styrylpyridine**, m.p. 217°, from 4-picoline (*Friedländer*, Ber. **38**, 2837).

2. HALOGEN DERIVATIVES OF PYRIDINE. Pyridines containing halogen in the nucleus are obtained with difficulty by the direct action of halogens on pyridines; in the homologous pyridines bromine especially replaces the hydrogen atoms in the side-chain (*cf. Knudsen*, Ber. **25**, 2985; **28**, 1759). The substitution of the pyridine hydrogen atoms is more readily accomplished by heating pyridine or hydroxypyridines with PCl_5 or $SbCl_5$.

When pyridine is heated with PCl_5 at 210 220° these products are obtained: 2,6-**dichloropyridine**, m.p. 88°, which is also prepared by decarboxylation of dichloroisonicotinic acid, three **trichloropyridines**, m.p. 50°, 68°, and 72°, 2,3,5,6-2,3,4,5-, and 2,3,4,6-**tetrachloropyridine**, m.p. 91°, 22°, and 75°, and, as the principal product, **pentachloropyridine**, C_5Cl_5N, m.p. 125°, which is also formed from pyridinediol or glutaconimide with PCl_5 (*cf.* p. 196) and, together with lower chlorination products, by prolonged treatment of pyridine hydrochloride with chlorine.

2-Chloropyridine, b.p. 166°, is prepared by the action of PCl_5 on 2-pyridol or, more advantageously, on N-alkylpyridones (p. 209). With $PBr_5 + POBr_3$, the N-alkylpyridones give **2-bromopyridine**, b.p. 193°. When 2-chloropyridine is treated with methyl iodide, **1-methyl-2-iodopyridinium iodide**, $C_5H_4IN(CH_3)I$, is formed (*Fischer*, Ber. **32**, 1297). **3-Chloro-** and **3-bromopyridine**, b.p. 148° and 170°, are obtained from potassium pyrrole with $CHCl_3$ and $CHBr_3$ (p. 30); 3-chloropyridine is also prepared from α-chloroglutaconaldehyde and NH_3 (*Dieckmann*, Ber. **38**, 1651). **2-Phenyl-6-chloropyridine**, m.p. 34°, from phenylpyridine (*Leben*, Ber. **29**, 1679). **4-Chlorolutidine**, b.p. 176° to 178°, from lutidone (*Michaelis*, *Hölken*, Ann. **331**, 254).

3. PYRIDINESULFONIC ACIDS. **3-Pyridinesulfonic acid**, $C_5H_4(SO_3H)N$, is obtained from pyridine with fuming sulfuric acid. Its sodium salt gives 3-cyanopyridine, the nitrile of nicotinic acid, when distilled with KCN, and 3-pyridol when fused with KOH. **2-Pyridinesulfonic acid**, m.p. 240°, **4-pyridinesulfonic acid**, m.p. 135°, and **4-lutidinesulfonic acid** are produced by oxidation of the corresponding mercaptans (p. 211) (*Marckwald*, *Klemm*, *Trabert*, Ber. **33**, 1556; *Koenig*, *Kinne*, Ber. **54**, 1357). When piperidine is heated with sulfuric acid both pyridine and pyridinesulfonic acids are formed.

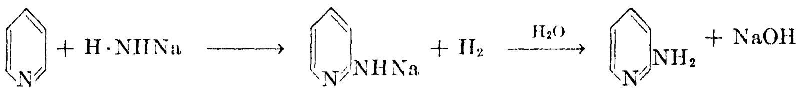
4. PYRIDINEARSINIC ACIDS. **3-Pyridinearsinic acid**, $C_5H_4N\cdot AsO(OH)_2$, m.p. 112°, from 2-chloro-3-aminopyridine by replacement of the amino group and subsequent removal of the chlorine (*Binz*, *Räth*, *Gante*, Ann. **467**, 11).

5. **NITROPYRIDINES.** The nitration of the pyridine nucleus is apparently possible only when NH_2, OH, or similar groups are present; these are the same groups which facilitate the nitration of benzene.

Nitration of 3-pyridol (p. 209) gives two **nitropyridols,** m.p. 211° and 295–298° (dec.), and **dinitropyridol,** m.p. 133° (*Weidel, Murmann,* Mo. **16,** 749). For nitroaminonicotinic acids, see nicotinic acid.

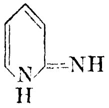
6. **AMINO-** and **HYDRAZINOPYRIDINES** can be prepared from 2- and 4- (but not 3-) halogenopyridines by treatment with NH_3 or N_2H_4. Aminopyridines are also obtained from pyridinecarboxylic acids: (*1*) by the action of KOBr on their amides (*Hofmann* reaction) [*Camps,* Arch.Pharm. **240** (1902), 345], or (*2*) by conversion of the acid azides to pyridylurethans with alcohol and decomposition of the latter (*Curtius* reaction).

The most convenient method of preparing 2-aminopyridine and its homologues was introduced by *Tschitschibabin;* it consists in the reaction of sodium amide with pyridine in boiling toluene [*Tschitschibabin, Seide,* J.Russ.Phys.Chem.Soc. **46** (1915), 1216; *Wibaut, Dingemanse,* Rec. **42,** 240; Ger. Pat. 358397, 1920, Frdl. **XIV,** 529; Ger. Pat. 362446, 1920, Frdl. **XIV,** 530; Ger. Pat. 374291, 1914, Frdl. **XIV,** 527]:



Some diaminopyridine is also formed.

The 3-aminopyridines resemble the anilines most closely, since they form diazo- and diazoamino compounds and azo dyes [*cf.* the reactions of diazotized 3-aminopyridine: *Tschitschibabin, Rjasanzew,* J.Russ.Phys.Chem.Soc. **47** (1916), 1571; *Tschitschibabin, ibid.* **50** (1919), 502, 512; *Tschitschibabin, Schemjakina, ibid.* **53** (1922), 217]. When treated with alkylating agents or with chloroacetic acid (*Tschitschibabin, Konowalowa, Konowalowa,* Ber. **54,** 814), 2-aminopyridine often reacts in the tautomeric form as 2-pyridoneimine:



(see the section on the tautomerism of the pyridine nucleus, p. 197).

2-Aminopyridine, m.p. 57°, b.p. 204°, is formed from 2-chloropyridine with zinc chloride-ammonia at 220° (*Fargher, Furness,* J. **107,** 688), from 2- or 6-aminonicotinic acid by decarboxylation and from picolinamide; it is prepared in very good yield from pyridine and sodium amide (see above). **2-Methylaminopyridine,** b.p. 200° (picrate, m.p. 190°), from the sodium derivative of 2-aminopyridine with methyl iodide (*Tschitschibabin, Konowalowa, Konowalowa,* Ber. **54,** 814). **2-Dimethylaminopyridine,** liquid (picrate, m.p. 182°) (*Tschitschibabin, Konowalowa,* Ber. **59,** 2055). For 1-methylpyridoneimine, see p. **209.** **2-Anilinopyridine,** m.p. 108°, from chloropyridine and aniline zinc chloride (*Fischer,* Ber. **35,** 3674). **2-Amino-3-methylpyridine,** *2-amino-3-picoline,* m.p. 26°, from 3-picoline with sodium amide (*Seide,* Ber. **57,** 1802). **2-Amino-4-methylpyridine,** *2-amino-4-picoline,* m.p. 104° (*Seide,* Ber. **58,** 1733). **2-Amino-6-methylpyridine,** *6-amino-2-picoline,* m.p. 41° (*Meyer,* Rec. **44,** 323).

3-Aminopyridine, m.p. 64°, b.p. 251° from nicotinamide with KOBr, from the corresponding nitro compound (*Kirpal, Reiter,* Ber. **58,** 699) and from 3-aminopicolinic acid (*Meyer,* Rec. **44,** 323); it is also formed in the decomposition of 3-pyridylurethan, $(C_5H_4N)NHCO_2C_2H_5$, m.p. 87°, and dipyridylurea, which are obtained from nicotinic acid azide (p. **214**) with alcohol or water (*Curtius, Mohr,* Ber. **31,** 2493). For pyridinediazonium salts, 2-diazoaminopyridine, $(C_5H_4N)N{:}N{\cdot}NH(C_5H_4N)$, and pyridineazoresorcinol see *Mohr,* Ber. **31,** 2495. **3-Amino-4-methylpyridine,** m.p. 106° (*Koenigs, Fulde,* Ber. **60,** 4106).

4-Aminopyridine, m.p. 155°, from isonicotinamide [*Camps,* Arch.Pharm. **240** (1902), 245] or from 4-aminodipicolinic acid by decarboxylation (*Tschitschibabin, Ossetrowa,* Ber. **58,** 1708). It often reacts in the tautomeric form as 4-pyridoneimine (p. 197). 4-**Amino-2,6-lutidine**, m.p. 186°, b.p. 246°, from the aminolutidinecarboxylic acid.

2,5-**Diaminopyridine** (*Meyer, Staffen*, Mo. **34**, 517; *Tschitschibabin, Kirsanow*, Ber. **60**, 766); 2,3-**diaminopyridine**, m.p. 112° (*Tschitschibabin, Kirsanow, loc. cit.* and *Konopnicki, Plazek*, Ber. **60**, 2045), both from the corresponding 2-aminonitropyridines. 3,5-**Diamino-2,6-dimethylpyridine**, m.p. 170°, from lutidinedicarboxylic acid diazide (*Mohr*, Ber. **33**, 1114).

2,2′-**Dipyridylamine**, m.p. 95.5° [*Wibaut, La Bastide*, Koninkl.Akad.Wettenschappen Amsterdam, wisk.natk.Afd. **36** (1927), 514].

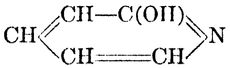
2- and 4-**Hydrazinopyridine**, m.p. 48°, b.p. 140° (20 mm.), from the corresponding halogenopyridines with hydrazine [*Fargher, Furness*, J. **107**, 688; *Tschitschibabin, Rasorenow*, J.Russ.Phys.Chem.Soc. **47** (1916), 1286; *Koenigs, Mields, Gurlt*, Ber. **57**, 1180]. 3-**Hydrazinopyridine**, m.p. 55°, from 3-pyridinediazonium chloride by reduction with $SnCl_2$ (Brit. Pat. 259961, 1926). 4-**Hydrazinolutidine**, m.p. 116°, from 4-chlorolutidine with hydrazine hydrate at 150°. With phenylhydrazine 4-chlorolutidine forms 4-**phenylhydrazinolutidine**, C_6H_5-$NHNH(C_7H_8N)$, which is converted by oxidation to **benzeneazolutidine**, C_6H_5-$N:N(C_7H_8N)$, m.p. 63° (*Marckwald, Rudzik*, Ber. **36**, 1111).

For **arsenopyridine**, **pyridinearsine**, $C_5H_4N \cdot AsH_2$, see *Binz, Röth, Gante*, Ann. **467**, 11.

7. HYDROXYPYRIDINES. The hydroxypyridines resemble the aminophenols in forming salts with both acids and bases. They are readily prepared by decarboxylation of the hydroxypyridinecarboxylic acids, most of which have been obtained from the corresponding pyrone derivatives (p. 177) with NH_3. The hydroxypyridines are generally colored red by ferric chloride. Like the phenols, 2- and 3-pyridols couple with diazonium salts to give *p*-hydroxy azo dyes.

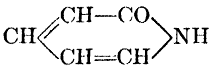
The 2- and 4-pyridols behave like cyclic imides or lactams. They must be considered as *oxo* derivatives of hydropyridines, or *pyridones*. For 2- and 4-monohydroxypyridines the following tautomeric formulas are possible:

(I)



$$CH\begin{matrix}\diagup CH-C(OH)\diagdown \\ \diagdown CH{=}CH\diagup\end{matrix}N$$

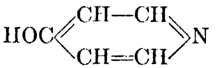
(Ia)



$$CH\begin{matrix}\diagup CH-CO\diagdown \\ \diagdown CH{=}CH\diagup\end{matrix}NH$$

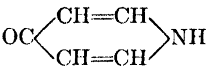
2-Pyridol, 2(1)-pyridone

(II)



$$HOC\begin{matrix}\diagup CH-CH\diagdown \\ \diagdown CH{=}CH\diagup\end{matrix}N$$

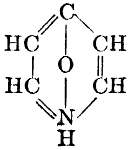
(IIa)



$$OC\begin{matrix}\diagup CH{=}CH\diagdown \\ \diagdown CH{=}CH\diagup\end{matrix}NH$$

4-Pyridol, 4(1)-pyridone

(III)

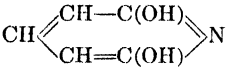


Derivatives of the hydroxyl form have been converted to the imine form. Thus, 2-*phenoxypyridine* is rearranged by passage of its vapors through a slightly incandescent tube into 1-*phenyl*-2(1)-*pyridone* (*Tschitschibabin, Jeletzky*, Ber. **57**, 1158).

For 1-aryl-4(1)-pyridones the phenolbetaine formula III has been proposed (*Fischer, Demeler*, Ber. **32**, 1308; *Smirnoff*, Helv. **4**, 599).

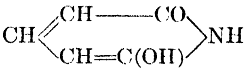
These formulas must be considered for the 2,6-pyridinediols or glutaconimides:

(I)



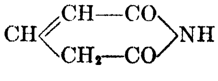
$$CH\begin{matrix}\diagup CH-C(OH)\diagdown \\ \diagdown CH{=}C(OH)\diagup\end{matrix}N$$

(II)



$$CH\begin{matrix}\diagup CH-CO\diagdown \\ \diagdown CH{=}C(OH)\diagup\end{matrix}NH$$

(III)

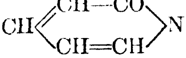


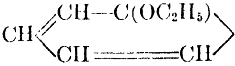
$$CH\begin{matrix}\diagup CH-CO\diagdown \\ \diagdown CH_2-CO\diagup\end{matrix}NH$$

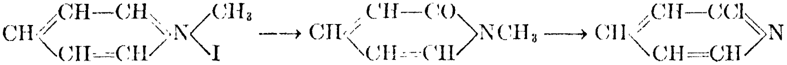
The members of this group are typical tautomeric compounds (see the section on tautomerism in Vol. I, p. 48).

In addition to the methods of preparation outlined above and the ring syntheses described on p. 199, hydroxypyridines can also be obtained by direct introduction of the hydroxyl group into the pyridine nucleus. This is accomplished by passage of the vapors over pulverized KOH heated to 300–320° (*Tschitschibabin*, Ber. **56**, 1882). This reaction, which evolves hydrogen, is analogous to the introduction of the amino group with $NaNH_2$ (see p. 207).

(*a*) *Monohydroxypyridines.*—2-**Pyridol**, 2(1)-**pyridone**, *α-pyridone*, m.p. 106°, b.p. 281°, mercuric chloride double salt, m.p. 192°, is prepared from its carboxylic acids, hydroxynicotinic acid and hydroxyquinolinic acid (p. **217**), or according to the methods given above. With bromine water it forms *dibromopyridol*, $C_5H_3Br_2ON$, m.p. 206°; with ethyl iodide it gives 1-*ethyl*-2(1)-*pyridone*,


$\mathrm{CH}\left\langle\begin{matrix}\mathrm{CH{-}CO}\\ \mathrm{CH{=}CH}\end{matrix}\right\rangle\mathrm{NC_2H_5}$, b.p. 247°, while its silver salt gives 2-*ethoxypyridine*,

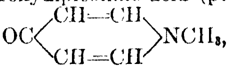

$\mathrm{CH}\left\langle\begin{matrix}\mathrm{CH{-}C(OC_2H_5)}\\ \mathrm{CH{=\!=\!=}CH}\end{matrix}\right\rangle\mathrm{N}$, b.p. 156°; with diazomethane 2(1)-pyridone forms 2-*methoxypyridine* (*v. Pechmann*, Ber. **28**, 1625). 1-*Methyl*-2(1)-*pyridone*, b.p. 166° (80 mm.), from 1-methyl-2-pyridoneimine by boiling with alkali (*Tschitschibabin, Konowalowa, Konowalowa*, Ber. **54**, 814). N-Alkyl-2(1)-pyridones are generally formed from 2-chloro-1-alkylpyridinium halides with aqueous sodium hydroxide and from 1-alkylpyridinium halides with aqueous sodium hydroxide and potassium ferricyanide (p. 201 and *Decker, Kaufmann*, J.pr. **84**, 435). When N-alkylpyridones are heated with phosphorus halides, alkyl halide is split off, leaving 2-halogenopyridines (p. 206) (*Fischer*, Ber. **32**, 1297):

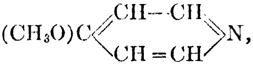

$$\mathrm{CH}\left\langle\begin{matrix}\mathrm{CH{-}CH}\\ \mathrm{CH{=}CH}\end{matrix}\right\rangle\mathrm{N}\left\langle\begin{matrix}\mathrm{CH_3}\\ \mathrm{I}\end{matrix}\right. \longrightarrow \mathrm{CH}\left\langle\begin{matrix}\mathrm{CH{-}CO}\\ \mathrm{CH{=}CH}\end{matrix}\right\rangle\mathrm{NCH_3} \longrightarrow \mathrm{CH}\left\langle\begin{matrix}\mathrm{CH{-}CCl}\\ \mathrm{CH{=}CH}\end{matrix}\right\rangle\mathrm{N}$$

2,4-**Dimethyl**-2(1)-**pyridone**, *pseudolutidostyril, mesitene lactam*, m.p. 180°, is prepared from dimethyl-1,2-pyrone or mesitene lactone (p. 178) with NH_3, and from its carboxylic acids. 6-**Phenyl**-2(1)-**pyridone**, m.p. 197°, from phenyl-1,2-pyrone with ammonium acetate; with aniline, 1,6-**diphenyl**-2(1)-**pyridone**, m.p. 145°, is formed (*Leven*, Ber. **29**, 1677).

3-**Pyridol**, m.p. 124°, distills undecomposed; it is obtained from 3-pyridinesulfonic acid by fusion with KOH or from 3-aminopyridine with nitrous acid. Its ethyl ether, $C_5H_4(OC_2H_5)N$, results from the reaction of alcoholic KOH with 3-bromopyridine.

4-**Pyridol**, 4(1)-**pyridone**, *γ-pyridone*, $C_5H_5ON(+H_2O)$, m.p. 148°, is prepared from its carboxylic acids, hydroxypicolinic acid and hydroxydipicolinic acid (p. 217). With methyl iodide it gives 1-methyl-4(1)-pyridone,


$\mathrm{OC}\left\langle\begin{matrix}\mathrm{CH{=}CH}\\ \mathrm{CH{=}CH}\end{matrix}\right\rangle\mathrm{NCH_3}$, m.p. 89°, and with diazomethane a mixture of 1-methyl-4(1)-pyridone and 4-methoxypyridine,


$\mathrm{(CH_3O)C}\left\langle\begin{matrix}\mathrm{CH{-}CH}\\ \mathrm{CH{=}CH}\end{matrix}\right\rangle\mathrm{N}$, b.p. 190° [*Peratoner, Azzarello*, Atti accad. Lincei **15** (1906), I, 139]. The latter is also formed from 4-chloropyridine with sodium methylate; unlike its isomer, it is decomposed by hydriodic acid into methyl iodide and 4(1)-pyridone.

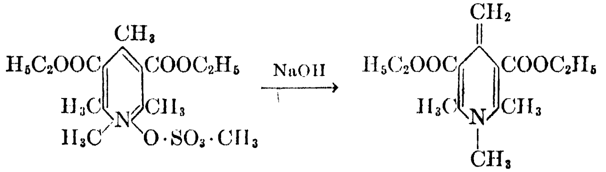
2,6-**Dimethyl**-4(1)-**pyridone**, 4-**lutidone**, m.p. 225°, is obtained from 2,6-dimethyl-4(1)-pyridonedicarboxylic acid (p. **217**) and from dehydroacetic acid (p. **178**) with NH_3 (*Sedgwick, Collie*, J. **67**, 399). It reacts with phenylhydrazine to form a phenylhydrazone, $(C_7H_9N)N{:}NNHC_6H_5$, m.p. 125° (*Petrenko-Kritschenko, Mosseschwili*, J.pr. **64**, 496).

1,2,6-**Trimethyl**-4(1)-**pyridone** is formed from 4-chloro-1-methyllutidinium iodide with dilute aqueous sodium hydroxide (*Michaelis, Holken*, Ann. **331**, 256). 4-**Ethoxylutidine**, b.p. 207°, from 4-aminolutidine (p. 208) by diazotization in alcoholic solution (*Marckwald*, Ber. **27**, 1328).

1-**Methyl**-2-**imino**-1,2-**dihydropyridine**, 1-*methyl*-2-*pyridoneimine*, picrate m.p. 201°, results from the action of methyl iodide on 2-aminopyridine (*Tschitschibabin*, *Konowalowa, Konowalowa*, Ber. **54**, 814); when heated it rearranges to 2-methylaminopyridine (*Reindel, Rauch*, Ber. **58**, 394).

Methylenedihydropyridines, Pyridone Methides.—Methylenedihydropyridines, which may be considered as derivatives of 2(1)- and 4(1)-pyridone, are produced by the action of alkali on the dimethyl sulfate or alkyl iodide addition products of 2- and 4-methylpyridines (I). In the case illustrated below, a series of intermediate steps culminate in the formation of two interconvertible methylenedihydropyridines (II and III), which correspond to the methylenequinones of the aromatic series. These compounds might also exist as free radicals (IV). The simplest members of this group, from 2- and 4-picoline, have not yet been reported (*Mumm, Hingst*, Ber. **56**, 2301; *Tschitschibabin, Benewolenskaja*, Ber. **61**, 547).

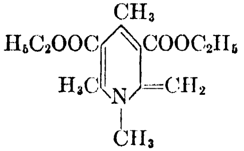
(I)



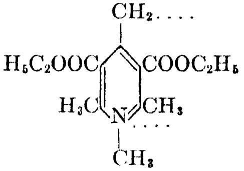
(II)

and

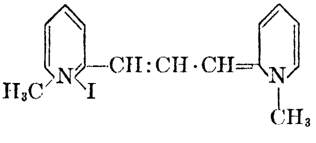
(III)



(IV)



The methylenedihydropyridines are intermediate products in the preparation of the pyridine analogues of the carbocyanines, which are formed by the action of sodium alcoholates on 1,2- and 1,4-dimethylpyridinium iodides in the presence of chloroform (*Rosenhauer, Barlet*, Ber. **62**, 2724):



1,1′-Dimethyl-2,2′-carbopyridinecyanine iodide

For other methylenedihydropyridines, see *Mumm*, Ann. **443**, 272.

(*b*) *Dihydroxypyridines.*—2,6-**Pyridinediol**, *glutaconimide*, $C_5H_5O_2N$, m.p. 184°, is prepared from hydroxyglutarimide, glutaconamic acid, glutaconamide or dihydroxydinicotinic acid (p. 217). Its salts (chloride + H_2O, sulfate + 2 H_2O) are decomposed by water. Distillation with zinc dust converts it to *pyridine*, PCl_5 converts it to *pentachloropyridine* (*cf.* p. 206).

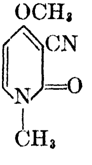
2,5-**Pyridinediol**, m.p. 248°, characterized by its blue coloration with ferric chloride, is obtained from 3-pyridol by fusion with NaOH (*cf.* p. 209). It is oxidized by MnO_2 and sulfuric acid to a pyridinequinone, $C_5H_3O_2N$ (*Kudernatsch*, Mo. **18**, 613).

Other isomeric dihydroxypyridines have been prepared by the fusion of pyridinedisulfonic acids with KOH (*Koenigs, Geigy*, Ber. **17**, 1832) and by the decarboxylation of comenamic acid and dihydroxypicolinic acid (p. 217) (*Weidel, Blau*, Mo. **6**, 651).

3-**Methyl-2,6-pyridinediol**, $C_5(CH_3)H_4O_2N$, m.p. 191°, 3-**ethyl-** and 3-**benzylpyridinediol** were synthesized from methyl-, ethyl-, and benzylglutaconic acid ester with ammonia (*Ruhemann*, J. **63**, 259, 874). 4-**Phenyl-2,6-pyridinediol**, m.p. 255° (*Ruhemann*, Proc.Chem.Soc. **1898/9**, No. 202, 6). These dihydroxypyridines correspond to resorcinol in the benzene series, and like it give *dyestuffs* with phthalic anhydride (*cf.* p. 202 and *Ruhemann*, Ber. **26**, 1559).

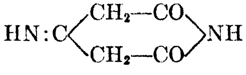
6-**Methyl-2,4-pyridinediol**, m.p. 331°, is obtained from the synthetic dihydroxypicolinic acid (p. 217). With N_2O_3 it yields a nitrosomethylpyridinediol, which is converted by treatment with stannous chloride and hydrochloric acid to **methylpyridinetriol**, m.p. 264° (*Hess*, Ber. **32**, 1985; *cf. Lapworth, Collie*, J. **71**, 838).

Ricinine, the poisonous alkaloid of the castor oil plants, has been identified as a derivative of a hydroxypyridone (*Späth*, Z.angew.Chem. **1928**, 1261):



Ricinine, 1-methyl-4-methoxy-3-cyano-2(1)-pyridone

(*c*) *Trihydroxypyridines*.—2,4,6-**Pyridinetriol**, *triketopiperidine*, decomposes at 220–230°; it corresponds to phloroglucinol. It is formed when glutazine is boiled with hydrochloric acid; this reaction is reversed when the trihydroxypyridine is heated with ammonia. **Glutazine**, *β-iminoglutarimide*,



$$HN{:}C\langle\begin{matrix}CH_2\text{—}CO\\CH_2\text{—}CO\end{matrix}\rangle NH$$

m.p. 300° (dec.), is obtained from β-oxoglutaric acid by warming with ammonia (*v. Pechmann*, Ber. **20**, 2655). An isomeric trihydroxypyridine, **pyromecazonic acid**, is formed by the reaction of pyromeconic acid (p. 179) with ammonia; it gives an indigo blue coloration with $FeCl_3$.

8. **PYRIDINETHIOLS.** Mercaptans of the pyridine series are prepared from 2- or 4-halogenopyridines by treatment with alcoholic KSH-solution (*Marckwald, Klemm, Trabert*, Ber. **33**, 1556). 2-**Pyridinethiol**, *thiopyridone*, yellow prisms, m.p. 125°, from 2-chloropyridine, is converted by iodine to a disulfide, $(C_5H_4N)_2S_2$, m.p. 58°, by nitric acid to pyridinesulfonic acid (p. 206) and by methyl iodide to **methyl 2-pyridyl sulfide**, b.p. 197°, which is also obtained by distillation of the methyl iodide addition product of 1-**methylthiopyridone**, $C_5H_4SN(CH_3)$, m.p. 90°. 1-Methylthiopyridone has been formed from 1-methyl-2-pyridone with P_2S_5 and from 2-iodo-1-methylpyridinium iodide with KSH (see above).

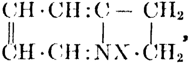
4-**Pyridinethiol**, m.p. 177°, yellowish white, from 4-chloropyridine and KSH (*Koenigs, Kinne*, Ber. **54**, 1357); the corresponding disulfide, colorless, m.p. 155°.

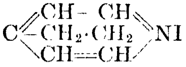
1-Methyliodopyridinium iodide reacts with potassium selenide to form 1-**methyl-2-selenopyridone**, $C_5H_4SeN(CH_3)$, m.p. 80°. The methyl iodide addition product of the latter is converted by distillation to **methyl 2-pyridyl selenide**, $(C_5H_4N)SeCH_3$, b.p. 212° (*Michaelis, Hölken*, Ann. **331**, 245).

2,6-**Dimethyl-4-pyridinethiol**, *thiolutidone*, m.p. 224°, from 4-chlorolutidine; *lutidyl sulfide*, $(C_7H_8N)_2S$, m.p. 83°; *disulfide*, m.p. 57°. The mercaptan is oxidized by alkaline H_2O_2-solution to 4-*lutidinesulfonic acid*. 1-**Methyl-4-thiolutidone**, m.p. 268°, from 4-chloro-1,2,6-trimethylpyridinium iodide with KSH, reacts with methyl iodide to form the methyl iodide addition product of 4-methylthiolutidine, $(C_7H_8N)SCH_3$, m.p. 51°, b.p. 233°. 1-Methyl-4-thiolutidone is oxidized by chlorine water to a trioxide, $C_7H_8N(CH_3)SO_3$ (*Michaelis, Hölken*, Ann. **331**, 245).

9. **PYRIDINE ALCOHOLS.** Pyridine alcohols or pyridine alkines are prepared: (*1*) from 2- and 4-alkylpyridines by aldol condensation with aldehydes; (*2*) from their hydrobromic acid esters, the homologous pyridines brominated in the side-chain, by heating with water; (*3*) from the corresponding ketones by reduction; and (*4*) by the action of alkylmagnesium compounds on the pyridine carboxaldehydes, which are difficult to obtain (*Lautenschläger, Onsager*, Ber. **51**, 602).

3-Pyridinemethanol, $C_5H_4N \cdot CH_2OH$, is obtained from its bromide, which is prepared from 3-picoline with bromine at 150° (*Dehnel*, Ber. **33**, 3498). 2-Methyl-5-(α-bromoethyl)pyridine when boiled with water yields **α,6-dimethyl-3-pyridinemethanol**, $C_5H_3(CH_3)NCH(OH)CH_3$, b.p. 240° (*Knudsen*, Ber. **28**, 1759). **α-Ethyl-2-pyridinemethanol**, $C_5H_4N \cdot CH(OH)C_2H_5$, b.p. 123–125° (20 mm.) (*Meisenheimer*, *Mahler*, Ann. **462**, 301); **α-phenyl-2- and -4-pyridinemethanol**, $C_5H_4N \cdot CH(OH)C_6H_5$, m.p. 82° and 126°, by reduction of 2-propionylpyridine and 2- and 4-benzoylpyridine with sodium amalgam (*Tschitschibabin*, Ber. **37**, 1370). **α,α-Dimethyl-2-pyridinemethanol**, $C_5H_4N \cdot C(OH)(CH_3)_2$, m.p. 51°, b.p. 204°, and **α,α-diethyl-2-pyridinemethanol**, b.p. 153° (24 mm.), are obtained from picolinic acid ester and alkylmagnesium halides (*Sobecki*, Ber. **41**, 4103).

The following alcohols were prepared by the condensation of 2- and 4-alkylpyridines with aldehydes (*Ladenburg*, Ber. **22**, 2583; Ann. **301**, 124; *Matzdorff*, Ber. **23**, 2709; *Bach*, Ber. **34**, 2233; *Koenigs*, *Happe*, Ber. **35**, 1343; **36**, 2904; *Lipp*, *Richard*, Ber. **37**, 737; *Lipp*, *Zerngibl*, Ber. **39**, 1045; *Löffler*, *Thiel*, Ber. **42**, 132): **2-Pyridineëthanol**, *picoline alkine*, $C_5H_4N \cdot CH_2CH_2OH$, b.p. 115° (9 mm.), **β-hydroxymethyl-2-pyridineëthanol**, **2-(β,β′-dihydroxyisopropyl)pyridine**, $C_5H_4N \cdot CH(CH_2OH)_2$, m.p. 78°, and **β,β-di-(hydroxymethyl)-2-pyridineëthanol**, **2-(β,β′,β″-trihydroxy-*t*-butyl)pyridine**, $C_5H_4N \cdot C(CH_2OH)_3$, m.p. 68°, are the products of the condensation of 2-picoline with formaldehyde. When heated with hydrobromic or hydriodic acid pyridineëthanol yields **2-β-bromo-** or **iodoethylpyridine**, $C_5H_4N \cdot CH_2CH_2X$, unstable oils, which readily rearrange to the high-melting bicyclic pyridinium salts,  $\begin{array}{l} CH \cdot CH : C - CH_2 \\ \| \qquad\quad | \quad\ \ | \\ CH \cdot CH : NX \cdot CH_2 \end{array}$, m.p. 213° and 227°, and which react with NH_3 and amines to form compounds such as **2-β-aminoethylpyridine**, $C_5H_4N \cdot CH_2CH_2NH_2$, b.p. 91° (12 mm.) (*Löffler*, Ber. **37**, 161; *Löffler*, *Kirschner*, Ber. **38**, 3329). 4-Picoline and formaldehyde give **4-pyridineëthanol**, $C_5H_4N \cdot CH_2CH_2OH$, b.p. 152° (14 mm.), picrate m.p. 135° (*Meisenheimer*, Ann. **420**, 202), and **β,β-di-(hydroxymethyl)-4-pyridineëthanol**, $C_5H_4N \cdot C(CH_2OH)_3$, **4-(β,β′,β″-trihydroxy-*t*-butyl)pyridine**, m.p. 156–157°. 2,6-Lutidine and formaldehyde give **6-methyl-2-pyridineëthanol** and **2,6-pyridinediethanol**, m.p. 55° and 74°. *s-Collidine* and formaldehyde give **β-hydroxymethyl-2,6-dimethyl-4-pyridineëthanol**, **2,6-dimethyl-4-(β,β′-dihydroxyisopropyl)pyridine**, $C_5H_2(CH_3)_2N \cdot CH(CH_2OH)_2$, m.p. 103°, and 2-ethylpyridine yields **β-methyl-2-pyridineëthanol**, $C_5H_4N \cdot CH(CH_3)CH_2OH$. The iodide from 4-pyridineëthanol and HI, like 2-iodoethylpyridine (see above) rearranges when heated to a bicyclic pyridinium salt:



(*Löffler*, *Steitzel*, Ber. **42**, 121). Reduction with hydriodic acid and phosphorus or with zinc dust converts these alcohols to the corresponding alkylpyridines, and oxidation transforms them to pyridinecarboxylic acids. **α-Methyl-2-pyridineethanol**, $C_5H_4N \cdot CH_2CH(OH)CH_3$, m.p. 32°, b.p. 124° (20 mm.), **α-phenyl-2-pyridineëthanol**, $C_5H_4N \cdot CH_2CH(OH)C_6H_5$, m.p. 97°, from picoline with acetaldehyde and benzaldehyde. **α-Trichloromethyl-2-pyridineëthanol**, m.p. 87°, from 2-picoline and chloral; for its reactions, see p. 202.

10. PYRIDINECARBOXALDEHYDES are difficult to prepare. Reduction of the corresponding acid chlorides yields small quantities of aldehydes [*Rojahn*, *Schulten*, Arch.Pharm. **264** (1926), 348].

11. PYRIDINE KETONES. Ketones of the pyridine series are prepared by distillation of Ca salts of pyridinecarboxylic acids with Ca salts of fatty or aromatic acids (*Hess*, *Munderloh*, Ber. **52**, 987) and by ring-synthesis (*Scholtz*, Ber. **30**, 2295; *Knoevenagel*, *Ruschhaupt*, Ber. **31**, 1025; *Benary*, *Psille*, Ber. **57**, 828). On reduction they form secondary alcohols and pinacones.

2-Acetylpyridine, b.p. 192°, from the Ca salt of picolinic acid and calcium acetate, *oxime*, m.p. 120°, *phenylhydrazone*, m.p. 155°; for condensation products with aromatic aldehydes, see *Engler*, *Engler*, Ber. **35**, 4061. **3-Acetylpyridine**, b.p. 220°, from the Ca salt of nicotinic acid and calcium acetate. **5-Acetyl-2-picoline**, b.p. 233°, from the corresponding alcohol (see above) by oxidation (*Knud-*

sen, Ber. **28**, 1764). **2-Propionylpyridine,** b.p. 205°, is reduced by Na and amyl alcohol to α-ethyl-2-piperidinemethanol, $C_2H_5CH(OH) \cdot C_5H_9NH$ (p. **224**), and then into (*d* + *l*)-coniine (p. **332**). **3-Benzoylpyridine,** $C_6H_5CO \cdot C_5H_4N$, b.p. 307° (*Bernthsen, Mettegang*, Ber. **20**, 1209), from benzoylpicolinic or isonicotinic acids (p. **215**), gives two isomeric oximes, m.p. 142° and 162°. **2-Benzoyl-** and **4-benzoylpyridine,** b.p. 317°, and m.p. 72°, b.p. 315°, from the benzylpyridines (p. **205**) by oxidation. **3,5-Diacetyl-2,6-lutidine,** $C_5H(COCH_3)_2(CH_3)_2N$, m.p. 74°, is prepared from 3,5-diacetyl-3-heptene-2,6-dione, $(CH_3CO)_2CHCH{:}C(COCH_3)_2$, with ammonia and from its dihydro derivative by oxidation with N_2O_3 (*Scholtz*, Ber. **30**, 2295; *Claisen*, Ann. **297**, 71). Other pyridine ketones have been similarly obtained from their dihydro derivatives, such as 3,5-**diacetyl-4-phenyl-2,6-lutidine,** m.p. 188°, from benzalacetonylacetone with aminoacetylacetone (*Knoevenagel, Ruschhaupt*, Ber. **31**, 1026). **2-Acetoacetylpyridine,** $C_5H_4N \cdot COCH_2COCH_3$, m.p. 50°, b.p. 137–143° (15 mm.), from picolinic acid ester, acetone, and sodium ethylate (*Weidel*, Mo. **17**, 401). **3-Acetoacetyl-** and **4-acetoacetylpyridine** are obtained by the same method from nicotinic and isonicotinic acid ester (*Tscherne*, Mo. **22**, 615).

12. PYRIDINECARBOXYLIC ACIDS. Carboxylic acids of the pyridine series are formed by ring-synthetic methods or by oxidation of homologous pyridines with potassium permanganate solution, alkyl and phenyl groups being converted to carboxyl groups (*cf.* p. 202); in condensed pyridine derivatives, such as quinoline and isoquinoline, the benzene ring leaves carboxyl groups when it is destroyed by oxidation. Therefore, most alkaloids, being derivatives of pyridine, quinoline, and isoquinoline, are converted to pyridinecarboxylic acids by energetic oxidation. In the preparation of these acids it must also be remembered that the pyridine ring itself is destroyed by oxidation on long boiling, especially with $KMnO_4$ (p. 202). For the separation of the acids produced from a mixture of pyridine bases, see *Pinner*, Ber. **33**, 1225.

The lower acids can be obtained from pyridinepolycarboxylic acids by heating with hydrochloric acid; the carboxyl groups in the 2- or 6-position are removed first. Heating with lime eliminates all the carboxyl groups, leaving pyridine.

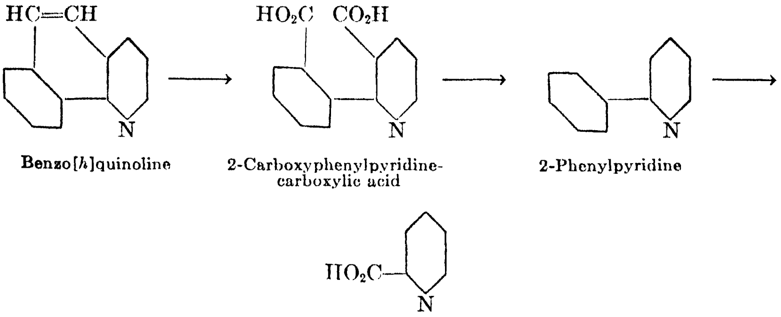
Like other pyridine derivatives, pyridinecarboxylic acids are reduced by sodium and alcohol to piperidinecarboxylic acids.

Several pyridinecarboxylic acids, when reduced with sodium amalgam in aqueous alkaline solution, are converted to *lactone acids* of the aliphatic series, the group $-CH{=}N \cdot CH{=}$ being transformed to $-CO{-}O{-}CH_2-$ (*Weidel, Hoff*, Mo. **13**, 578; *Perlmutter*, Mo. **13**, 840; *Smoluchowsky*, Mo. **15**, 55).

Since the pyridines are bases, their carboxylic acids behave like amino acids. In the polycarboxylic acids the basic properties are less pronounced. When pyridinecarboxylic acids are warmed with alkyl iodides in soda solution, *betaines* are formed (*Meyer*, Ber. **36**, 616).

As already mentioned on p. 203, the determination of the constitution of pyridine derivatives is based on the pyridinecarboxylic acids, since the position of substituents can usually be found by conversion to the carboxylic acids. An unequivocal proof of the constitution of the pyridinecarboxylic acids is therefore of major importance.

The Constitution of Pyridinemonocarboxylic Acids.—The constitution of 2-pyridinecarboxylic acid (picolinic acid) and 3-pyridinecarboxylic acid (nicotinic acid) is known through their preparation from 2- and 3-phenylpyridine by oxidation; 2-phenylpyridine and 3-phenylpyridine are obtained from benzo[*h*]- and benzo[*f*]quinoline, which oxidize to 2- and 3-phenylpyridinedicarboxylic acid, from which the phenylpyridines are formed by decarboxylation. This proof of constitution depends on the proof of the constitution of the benzoquinolines (p. **247**). The derivation of the constitution of picolinic acid is outlined by the following scheme:



Benzo[*h*]quinoline 2-Carboxyphenylpyridinecarboxylic acid 2-Phenylpyridine

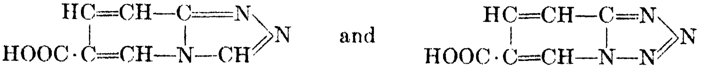
2-Pyridinecarboxylic acid, Picolinic acid

A simpler proof of the constitution is given by the behavior of pyridinedicarboxylic acids. Quinolinic acid (pyridinedicarboxylic acid), produced by the oxidation of quinoline, has the carboxyl groups in the 2,3-position, and cinchomeronic acid, from isoquinoline, is the 3,4-dicarboxylic acid. When quinolinic acid is heated, nicotinic acid is formed by elimination of one CO_2-group, but cinchomeronic acid gives both nicotinic and isonicotinic acid. Therefore nicotinic acid is 3-pyridinecarboxylic acid, and isonicotinic acid is 4-pyridinecarboxylic acid.

(*a*) *Pyridinemonocarboxylic Acids.*—2-**Pyridinecarboxylic acid, picolinic acid,** C_5H_4N-2-COOH, m.p. 135–138°, sublimable, is prepared by oxidation of 2-picoline (*Wibaut,* Rec. **45**, 662); it is colored *yellow-red* by ferrous sulfate, like all pyridinecarboxylic acids which contain a COOH-group in the 2-position. *Ethyl ester,* b.p. 243°; *chloride,* m.p. 47° (*Meyer, Graf,* Ber. **61**, 2202); *anhydride,* m.p. 124°; *amide,* m.p. 107°; *nitrile,* m.p. 29°, b.p. 212–215° [*Meyer,* Mo. **23**, 437; *Camps,* Arch.Pharm. **240** (1902), 366].

NICOTINIC ACID, 3-**pyridinecarboxylic acid,** m.p. 229°, first obtained from the alkaloid nicotine (p. 336), is prepared from 3-picoline and other 3-alkylpyridines, and from its nitrile (p. 206). Its methyl iodide addition product forms a betaine, $\overline{OCO\cdot C_5H_4N}\cdot CH_3$, which is identical with the alkaloid *trigonelline* (p. 331). Nicotinic acid *ethyl ester,* b.p. 218°; *chloride,* m.p. 16° (dec.) (*Meyer, Graf,* Ber. **61**, 2202); *amide,* m.p. 125°; *nitrile,* m.p. 49°, b.p. 240–245° [*Camps,* Arch.Pharm., **240** (1902), 366; *Meyer,* Mo. **23**, 897]; *hydrazide,* m.p. 159°; *azide,* m.p. 48° (*Curtius, Mohr,* Ber. **31**, 2493).

6-**Chloronicotinic acid,** 6-*chloropyridine*-3-*carboxylic acid,* m.p. 199°, from hydroxynicotinic acid (p. 217), reacts with NH_3, when heated, to give 6-**aminonicotinic acid,** which yields 2-aminopyridine on heating and 5-**nitro-6-aminonicotinic acid,** m.p. 280°, on nitration; by reduction of the latter, 5,6-**diaminonicotinic acid** is formed. 2-**Aminonicotinic acid,** from quinolinamic acid with KOBr, gives 2-aminopyridine when heated and a **nitroaminonicotinic acid** when nitrated (*Marckwald,* Ber. **27**, 1317; *Philips,* Ann. **288**, 253). With hydrazine 6-chloronicotinic acid forms 6-**hydrazinonicotinic acid,** COOH[3]C_5H_3N[6]-$NHNH_2$, m.p. 283°, which is converted by boiling with formic acid into *s*-triazolo[*a*]pyridinecarboxylic acid, and by HNO_2 into tetrazolo[*a*]pyridinecarboxylic acid:



$$\begin{array}{l}HC{=}CH{-}C{=}N\diagdown\\ \quad\ \ |\qquad\quad\ \ |\qquad\quad >N\\ HOOC\cdot C{=}CH{-}N{-}CH\diagup\end{array}\quad \text{and} \quad \begin{array}{l}HC{=}CH{-}C{=}N\diagdown\\ \quad\ \ |\qquad\quad\ \ |\qquad\quad >N\\ HOOC\cdot C{=}CH{-}N{-}N\diagup\end{array}$$

When oxidized these acids yield triazole (p. 153) and tetrazole (p. 170) (*Marckwald, Rudzik,* Ber. **36**, 1111).

ISONICOTINIC ACID, **4-pyridinecarboxylic acid**, m.p. 304°, from 4-methylpyridine and from cinchomeronic acid (see below) by decarboxylation (*Ternájgó*, Mo. **21**, 446). *Chloride*, m.p. 16° (*Meyer*, *Graf*, Ber. **61**, 2202); *ethyl ester*, b.p. 218°, whose ethyl iodide addition product decomposes to isonicotinic acid ethylbetaine, m.p. 241° (dec.); *amide*, m.p. 155°; *nitrile*, m.p. 79° [*Camps*, Arch. Pharm. **240** (1902), 366].

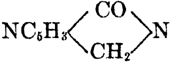
Homologous Pyridinemonocarboxylic Acids. 6-**Methylpicolinic acid**, $C_5H_3N[2,6](CH_3)COOH$, m.p. 85°, from 2,6-lutidine (*Ladenburg*, *Scholtze*, Ber. **33**, 1081; *Pinner*, *Lewin*, Ber. **33**, 1230). 2-**Methylisonicotinic acid**, sublimable, from 6-methyl-2,4-pyridinedicarboxylic acid (p. **216**) by decarboxylation. 4-**Methylnicotinic acid**, m.p. 210°, from 4-methylquinolinic acid (p. **216**) by decarboxylation. **2,4-Dimethylnicotinic acid**, $C_5(CH_3)_2H_2N \cdot COOH$ (+2 H_2O), is obtained in the form of its ester from acetoacetic ester with 2 mols of acetaldehyde and NH_3 according to method *2* (p. 198). **2,6-Dimethyl-4-chloronicotinic acid**, $C_5HCl(CH_3)_2N[3]COOH$, m.p. 168–170°, from β-aminocrotonic acid ester by heating with $POCl_3$, reacts with hydrazine and phenylhydrazine to give hydrazine derivatives, which form bicyclic pyrazolones by elimination of water (*Michaelis*, *Arend*, Ber. **36**, 515; *Michaelis*, Ann. **366**, 324).

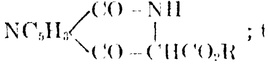
2,6-Diphenylisonicotinic acid, m.p. 279°, from diphenacylacetic acid with NH_3 (*Klobb*, Bull. [3] **29**, 407).

(*b*) *Pyridinedicarboxylic Acids.* **QUINOLINIC ACID**, **2,3-pyridinedicarboxylic acid**, $C_5H_3N(COOH)_2$, m.p. 190° (dec.) is prepared from quinoline and quinolines substituted in the benzene nucleus by oxidation with potassium permanganate in alkaline (*Hantzsch*, Ber. **19**, 293) or, more advantageously, in alkaline-earth solution (Ger. Pat. 414072, 1923, Frdl. **XV**, 1486). For the esterification of quinolinic acid, see *Kirpal*, Mo. **29**, 227. Quinolinic acid *anhydride*, m.p. 134°; *imide*, m.p. 230° (*Philips*, Ann. **288**, 257). The methyl iodide addition product of the anhydride is converted by treatment with Ag_2O and water to quinolinic acid methylbetaine, $\overline{OCO[3](CO_2H)[2]C_5H_3N}(CH_3)$; with benzene and $AlCl_3$ the anhydride yields 3-benzoylpicolinic acid, $C_5H_3N[3]COC_6H_5[2]COOH$ (*Kirpal*, Mo. **27**, 371; *Halla*, Mo. **32**, 747). In the same way the *quinolineins*, dyestuffs analogous to the phthaleins, are produced (*Ghosh*, J. **115**, 1101).

CINCHOMERONIC ACID, **3,4-pyridinedicarboxylic acid**, m.p. 266° (dec.), from cinchonine, cinchonidine, and quinine (*cf. Ternájgó*, Mo. **21**, 446) with nitric acid, from isoquinoline (p. 251) with $KMnO_4$, *etc.* It is reduced by sodium amalgam to *cinchonic acid*, $C_7H_8O_6$, which decomposes when heated into CO_2 and *pyrocinchonic acid* or dimethylmaleic acid anhydride (*Ladenburg*, Ber. **18**, 2968). Cinchomeronic acid *anhydride*, m.p. 67°, adds methyl alcohol to form the 4-*methyl ester*, $C_5H_3N[3]COOH[4]COOCH_3$, m.p. 173°, which, by conversion to the 4-*monoamide* (*cf. Gabriel*, *Colman*, Ber. **35**, 2841) and subsequent treatment with KOBr, yields 4-aminonicotinic acid. The *dimethyl ester*, b.p. 169–171° (28 mm.), can be partially saponified to the 3-*monomethyl ester*, $C_5H_3N[4]COOH[3]COOCH_3$. The 4-monomethyl ester is converted by treatment with methyl iodide and silver oxide to the methyl ester of apophyllenic acid, $\overline{OCO[3]CO_2CH_3[4]C_5H_3N}(CH_3)$ (*cf.* narcotine), while the 3-monomethyl ester gives the methyl ester of the isomeric cinchomeronic acid methylbetaine (*Kirpal*, Mo. **24**, 519). With benzene and $AlCl_3$ the anhydride yields a mixture of 4-benzoylnicotinic acid and 3-benzoylisonicotinic acid (*Kirpal*, Mo. **30**, 355).

Several 2,6-dialkylcinchomeronic acid esters are readily synthesized from β-aminocrotonic acid ester, acetoneoxalic ester and similar compounds (*Mumm*, *Hüneke*, Ber. **50**, 1568; *Mumm*, *Böhme*, Ber. **54**, 726; see method *2*, example (*b*), p. 198).

Cinchomeronimide, m.p. 230°, is converted by bromine lye into 3-aminoisonicotinic acid, which, like anthranilic acid, tends to form heterocyclic orthocondensation products (*Gabriel*, *Colman*, Ber. **35**, 2836). It is reduced by Sn and hydrochloric acid to cinchomeronimidine, 
$NC_5H_3\left\langle\begin{matrix}CO\\CH_2\end{matrix}\right\rangle NH$, m.p. 199–200°. N-(Carboethoxymethyl)-cinchomeronimide, $C_5H_3N(CO)_2NCH_2COOR$, from the potassium derivative of cinchomeronimide and chloroacetic ester, reacts with sodium ethylate similarly to the analogous phthalimide derivative, forming

a derivative of *copyrine* (containing two pyridine nuclei), **dihydroxycopyrinecarboxylic acid ester,**  $NC_5H_3\left\langle\begin{array}{l}CO-NH\\ \qquad\;|\\ CO-CHCO_2R\end{array}\right.$; the latter yields, on decarboxylation, **dihydroxycopyrine** and, on heating with hydriodic acid and phosphorus, 4-ethylnicotinic acid (*Gabriel, Colman*, Ber. **35**, 1358, 2831; *Fels*, Ber. **37**, 2129).

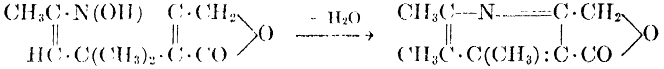
2,4-**Pyridinedicarboxylic acid, lutidinic acid,** $C_5H_3N(COOH)_2 + 2H_2O$, m.p. 235° (*Ladenburg*, Ann. **247**, 37). 2,5-**Pyridinedicarboxylic acid,** *isocinchomeronic acid*, crystallizes with 1 to 1½ H_2O, m p. 236° (*Weiss*, Ber. **19**, 1311). 2,6-**Pyridinedicarboxylic acid, dipicolinic acid,** m.p. 225° (*Ladenburg*, Ann. **247**, 33). 3,5-**Pyridinedicarboxylic acid, dinicotinic acid,** m.p. 314° (*Hantzsch, Weiss*, Ber. **19**, 286).

Homologous Pyridinedicarboxylic Acids. 4-**Methylquinolinic acid,** *lepidinic acid*, $C_5(CH_3)H_2N(COOH)_2$, m.p. 186°, from 4-methylquinoline (lepidine) or, better, from *Bz*-hydroxy-2-chlorolepidine by oxidation with $KMnO_4$; in the latter case, 2-chlorolepidinic acid is formed first, and this is reduced with HI and phosphorus to lepidinic acid (*Besthorn, Byvanck*, Ber. **31**, 796).

Uvitonic acid, 6-**methyllutidinic acid,** 6-**methyl**-2,4-**pyridinedicarboxylic acid,** $C_5(CH_3)H_2N(COOH)_2$, m.p. 244°, is formed by the action of alcoholic NH_3 on pyruvic acid.

Lutidinedicarboxylic acid, 2,6-*dimethyl*-3,5-*pyridinedicarboxylic acid*, $C_5H(CH_3)_2N(COOH)_2$, m.p. 316°, from methenyl-*bis*-acetoacetic ester with ammonia directly or by oxidation of the dihydro derivative first formed with N_2O_3 (*Weber*, Ann. **241**, 31; *Knoevenagel*, Ann. **281**, 94). For the hydrazide and azide, see *Mohr*, Ber. **33**, 1114.

Trimethylquinolinic acid, $C_5(CH_3)_3N[2,3](COOH)_2$, m.p. 195° (dec.), is formed by the oxidation of 2,3,4-trimethyl-5-oxo-5,7-dihydrofuro[3,4-*b*]pyridine (trimethylquinolide), m.p. 152°, which is obtained from the condensation product of tetronic acid (p. **22**) with mesityl oxide:



2,3,4- Trimethyl-5-oxo-5,7-dihydrofuro[3,4-*b*] pyridine

The trimethylquinolinic acid can be oxidized further to **dimethylpyridine**-2,3,5-**tricarboxylic acid** and 4-**methylpyridinetetracarboxylic acid,** which yield various lower carboxylic acids on decarboxylation (*Wolff*, Ann. **322**, 351).

2,4,6-**Trimethylpyridine**-3,5-**dicarboxylic acid,** *collidinedicarboxylic acid*, is obtained in the form of its ester from the synthetic dihydrocollidinedicarboxylic acid ester (p. 198) by oxidation with N_2O_3 and serves as starting material for a series of higher and lower pyridinecarboxylic acids.

(*c*) *Pyridinetricarboxylic acids.* 2,3,4-**Pyridinetricarboxylic acid,** *carbocinchomeronic acid*, $C_5H_2N(COOH)_3 + 1H_2O$, m.p. 250° (238°: *Eckert, Loria*, Mo. **38**, 243), is formed from quinine, cinchonine, and various conversion products of these alkaloids, and also from 4-methylquinolinic acid (see above) by oxidation with $KMnO_4$. For the esterification of this acid, see *Rint*, Mo. **18**, 223; *Kirpal*, Mo. **26**, 53. 2,4,6-**Pyridinetricarboxylic acid,** m.p. 227° (dec.), from *s*-collidine or 6-methyllutidinic acid (see above) (*Voigt*, Ann. **228**, 29). 2,4,5-**Pyridinetricarboxylic acid,** *berberonic acid* ($+2H_2O$), m.p. 243°, from the alkaloid berberine with nitric acid (*Mayer*, Mo. **13**, 344). 2,3,6-**Pyridinetricarboxylic acid** ($+ 2H_2O$), dec. 130° (*Weiss*, Ber. **19**, 1309; *Eckert, Loria*, Mo. **38**, 243).

(*d*) *Pyridinetetracarboxylic Acids.* 2,3,4,6-**Pyridinetetracarboxylic acid,** + 3 H_2O, m.p. 235° (anhyd.), is prepared from 2,4,6-trimethylnicotinic acid or from 2,6-dimethylcinchomeronic acid (p. **215**) by oxidation with $KMnO_4$ (*Michael*, Ann. **225**, 122; *Mumm, Hüncke*, Ber. **51**, 160). For the 2,3,5,6-tetracarboxylic acid and others, see *Hantzsch, Weiss*, Ber. **19**, 284; *Weiss*, Ber. **19**, 1309.

(*e*) **Pyridinepentacarboxylic acid,** $C_5N(COOH)_5 + 2H_2O$, dec. 220°, is formed by oxidation of collidinedicarboxylic acid.

13. HYDROXYPYRIDINECARBOXYLIC ACIDS. The statements made concerning the constitution of the hydroxypyridines or pyridones on p. 208 hold also for the hydroxypyridinecarboxylic acids. The latter are readily obtained from the corresponding pyronecarboxylic acids (p. 179) with ammonia, as well as by various other ring-synthetic methods. They are also formed by the action of CO_2 (at 180–200° and 20 atm.) on the sodium salts of hydroxypyridines (*Tschitschibabin*, *Kirssanow*, Ber. **57**, 1161); *cf.* the *Kolbe-Schmitt* salicylic acid synthesis. When heated they generally decompose into CO_2 and pyridones.

(*a*) *Monohydroxypyridinecarboxylic Acids.*—6-**Hydroxypyridine-3-carboxylic acid**, 6-*hydroxynicotinic acid*, $C_5H_4ON(COOH)$, m.p. 303°, is prepared from 1,2-pyrone-5-carboxylic acid ester (p. 178) with ammonia, from hydroxyquinolinic acid (see below) by decarboxylation and from the sodium salt of 2-pyridol by treatment with CO_2 (*Tschitschibabin*, *Kirssanow*, Ber. **57**, 1161). 2-**Hydroxypyridine-3-carboxylic acid**, 2-*hydroxynicotinic acid*, m.p. 255° (dec.), from 2-aminonicotinic acid (p. 214) and by various other methods (*Philips*, Ann. **288**, 265; *Weidel*, *Georgievics*, Mo. **9**, 145). 4-**Hydroxypyridine-3-carboxylic acid**, 4-*hydroxynicotinic acid*, m.p. 250° (dec.), from 4-aminonicotinic acid (*Kirpal*, Mo. **23**, 246). 4-**Hydroxypyridine-2-carboxylic acid**, 4-*hydroxypicolinic acid* (+ H_2O), m.p. 250°, from 1,4-pyrone-2-carboxylic acid (p. 179) with NH_3. 6-**Hydroxypyridine-2,3-dicarboxylic acid**, 6-*hydroxyquinolinic acid*, $C_5H_3ON(COOH)_2$, dec. 254°, is obtained from quinolinic acid by fusion with KOH or from its methyl ether, methoxyquinolinic acid, m.p. 140°, which is formed by the oxidation of aminocarbostyril methyl ether with $KMnO_4$. 6-**Hydroxylepidinic acid**, $C_5H_2ON(CH_3)(COOH)_2$, from dihydroxylepidine (*Besthorn*, *Byvanck*, Ber. **31**, 802). 4-**Hydroxypyridine-2,6-dicarboxylic acid**, *hydroxydipicolinic acid ammonchelidonic acid*, *chelidamic acid*, from chelidonic acid (p. 179) with NH_3.

2,4-**Dimethyl-6-hydroxypyridine-3-carboxylic acid**, *pseudolutidostyrilcarboxylic acid*, $C_5(CH_3)_2H_2ON(COOH)$, is produced by heating β-aminocrotonic acid ester hydrochloride to 120° (*Collie*, J. **59**, 172). When β-anilinocrotonic acid ester is heated, **N-phenyllutidonecarboxylic acid**, 2,6-**dimethyl-1-phenyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid**, $C_5H(CH_3)_2(C_6H_5)ON(COOH)$, and 2-methyl-4-quinolinol (p. 239) are formed. 2,6-**Lutidone-3,5-dicarboxylic acid**, 2,6-**dimethyl-4-hydroxypyridine-3,5-dicarboxylic acid**, m.p. 267°, is prepared from dimethylpyronedicarboxylic acid ester (p. 150) with NH_3; with PCl_5 it gives 4-**chlorolutidinedicarboxylic acid**, m.p. 224°, which reacts with NH_3 at 130° to form 4-**aminolutidinedicarboxylic acid** (*Marckwald*, Ber. **27**, 1323).

(*b*) *Dihydroxypyridinecarboxylic Acids.*—4,5-**Dihydroxypicolinic acid**, **comenamic acid**, is prepared by heating 5-hydroxypyrone-2-carboxylic acid (p. 180) with NH_3. 2,4-**Dihydroxy-6-methylnicotinic acid**, $C_5H_3(CH_3)O_2N(COOH)$, is obtained in the form of its ester by condensation of equimolar proportions of malonic ester and β-aminocrotonic acid ester in the presence of sodium ethylate. 2,6-**Dihydroxynicotinic acid**, m.p. 198°, from isaconitic acid ester, $(COOR)_2CH\cdot CH:CHCOOR$, with NH_3, is converted by PCl_5 into *dichloronicotinic acid*, m.p. 144° (*Guthzeit*, *Laska*, J.pr. **58**, 433). 2,6-**Dihydroxydinicotinic acid**, $C_5H_3O_2N(COOH)_2$, has been obtained in the form of its ester and ether from dicyanoglutaconic acid ester, $COORC(CN):CH\cdot CH(CN)COOR$, and from 6-ethoxy-1,2-pyrone-3,5-dicarboxylic acid ester with ammonia; it gives **dichlorodinicotinic acid ester**, m.p. 76° (*Errera*, Ber. **31**, 1241; *Gutzeit*, Ber. **32**, 779; *Ruhemann*, *Browning*, J. **73**, 280; *Claisen*, Ann. **297**, 87). 2,6-**Dihydroxyisonicotinic acid**, *citrazinic acid*, by warming citramide, $CONH_2C(OH)(CH_2CONH_2)_2$, with H_2SO_4. 2,6-Dichloroisonicotinic acid reacts with aniline to give 2,6-dianilinoisonicotinic acid and with KSH to give 2,6-dimercaptoisonicotinic acid, $C_5H_2N(SH)_2COOH$, m.p. 230° (*Bittner*, Ber. **35**, 2933). With chloroform and alkali citrazinic acid forms a **formyldihydroxypyridinecarboxylic acid** (*Sell*, J. **69**, 1447).

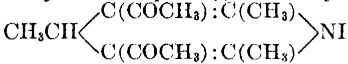
2-**Methyl-5,6-dihydroxyisonicotinic acid**, from chloroacetone, oxaloacetic ester, and NH_3.

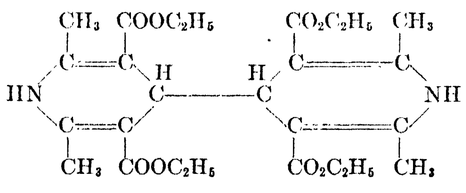
14. Only a few **FATTY ACIDS SUBSTITUTED BY PYRIDYL GROUPS** are known. 2,3,5-**Trichloro-4-pyridineacetic acid**, $(C_5Cl_3HN)CH_2COOH$, m.p. 145°, produced by the condensation of tetrachloropyridine and sodium malonic ester to trichloropyridinemalonic ester and decarboxylation of the latter, is converted by heat to methyltrichloropyridine (*Sell*, *Dootson*, J. **83**, 396). Because

of their relation to the alkaloids, several pyridinelactic acids have been investigated: **α-picolinelactic acid**, $C_5(CH_3)H_3N \cdot C(OH)(CH_3)COOH$, is obtained from its nitrile, the cyanhydrin of 5-acetyl-2-picoline (p. 212) (*Knudsen*, Ber. **28**, 1765). **β-2-Pyridinelactic acid**, $C_5H_4N \cdot CH_2CH(OH) \cdot COOH$, m.p. 125°, is prepared from its orthochloride, α-trichloromethyl-2-pyridineëthanol, $C_5H_4N \cdot CH_2CH(OH)CCl_3$, (p. 212), with soda. When the latter compound is treated with alcoholic KOH, **2-pyridineacrylic acid**, $C_5H_4N \cdot CH:CHCOOH$, is formed. This acid is converted by reduction to **pyridinepropionic acid**, m.p. 141°, by bromine to pyridinedibromopropionic acid, and by hydrogen bromide to β-bromo-2-pyridinepropionic acid, $C_5H_4N \cdot CHBr \cdot CH_2COOH$ [*Einhorn*, Ann. **265**, 221; *Feist*, Arch.Pharm. **240** (1902), 178]. **α-Methylene-2-picolineacetic acid**, $C_5(CH_3)H_3N \cdot C(:CH_2)COOH$, is prepared from picolinebromopropionic acid, the product of the reaction of PBr_3 on α-picolinelactic acid. 2-, 3- and 4-**Pyridylformylacetic esters**, $(C_5H_4N)COCH_2CO_2C_2H_5$, are formed from the pyridinecarboxylic acid esters with acetic ester and sodium ethylate; they give the characteristic reactions of β-oxocarboxylic acid esters (*Pinner*, Ber. **34**, 4234).

Hydropyridine Derivatives

Hydropyridines are prepared by reduction of pyridines with zinc and hydrochloric acid or, more advantageously, with sodium and boiling alcohol, also by electrolytic [*Marie*, *Lejeune*, J.chim.phys. **22** (1925), 59] and catalytic reduction (*Zelinsky*, *Borisoff*, Ber. **57**, 150; *Hamilton*, *Adams*, Am. **50**, 2260). The products are almost always the completely hydrogenated derivatives, **piperidines.**

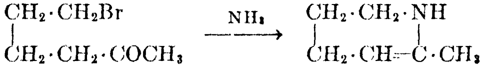
(*a*) **DIHYDROPYRIDINES** are synthesized from β-dioxo compounds with aldehydes and NH_3 (p. 198); *cf.* dihydrocollidinedicarboxylic acid ester, dihydrolutidinedicarboxylic acid ester (from formaldehyde, acetoacetic ester, and NH_3), dihydrodiacetyllutidine (p. 213), and many others. **1,4-Dihydro-3,5-diacetyl-s-collidine,**  $CH_3CH\left\langle\begin{matrix}C(COCH_3):C(CH_3)\\C(COCH_3):C(CH_3)\end{matrix}\right\rangle NH$, m.p. 152°, is obtained from ethylideneacetylacetone with aminoacetylacetone. The partial hydrogenation of pyridine derivatives to dihydropyridines can be accomplished easily only with carboxylic acid esters (with aluminum amalgam in undried ether). The dihydro products thus formed are sometimes identical to, sometimes isomeric with those prepared by ring-synthesis (*Mumm*, *Beth*, Ber. **54**, 1592). These reductions also yield **1,4,1′,4′-tetrahydro-4,4′-bipyridines,** such as:



These compounds are derived from two molecules of the pyridine derivative by addition of two hydrogen atoms (*Mumm*, *Beth*, Ber. **54**, 1595). **1,1′-Dialkyl-1,1′,4,4′-tetrahydro-4,4′-bipyridines** are produced by reduction of N-alkylpyridinium methyl sulfates with sodium amalgam in a CO_2-atmosphere (*Mumm*, *Rodev*, *Ludwig*, Ber. **57**, 865; *Mumm*, *Ludwig*, Ber. **59**, 1605).

These dihydro derivatives are usually readily oxidized to pyridines with N_2O_3 or dilute nitric acid. The dihydrolutidinedicarboxylic acid ester is transformed by treatment with hydrochloric acid to lutidinedicarboxylic acid ester and hexahydrolutidinedicarboxylic acid ester (*Knoevenagel*, *Fuchs*, Ber. **35**, 1788). When boiled with alkali the dihydropyridines decompose with evolution of ammonia; the fission products partially condense to carbocyclic rings. With concentrated alkali dihydrocollidinedicarboxylic acid ester is converted first to the *monocarboxylic acid* ester and then to *dihydrocollidine* (*Knoevenagel*, *Ruschhaupt*, Ber. **31**, 1025; *Cohnheim*, Ber. **31**, 1033).

(*b*) **TETRAHYDROPYRIDINES, PIPERIDEINES,** are formed, together with much larger yields of piperidines, by the reduction of pyridines with sodium and alcohol. They can be isolated by means of their dibromides, from which they are regenerated by treatment with zinc dust and sulfuric acid. The bases so obtained are 1,2,5,6-tetrahydropyridines. They can be reduced to piperidines only with strong agents such as HI and phosphorus. With acid chlorides and aqueous sodium hydroxide they form N-acyl derivatives (*Koenigs, Bernhart,* Ber. **38,** 3042, 3928; *Koenigs,* Ber. **40,** 3199). On the other hand, the 1,2,3,4-*tetrahydropyridines,* synthesized from the unstable δ-amino ketones or from δ-bromo ketones with ammonia or primary amines (*Lipp,* Ann. **289,** 173; **294,** 135; *cf. Ladenburg,* Ann. **304,** 54; *Sachs,* Ber. **32,** 61):

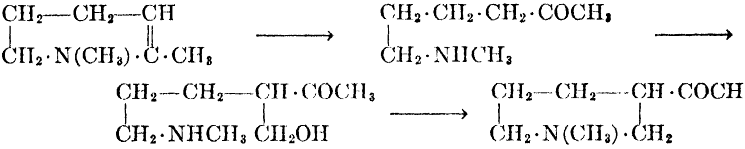


$$\begin{array}{l}CH_2\cdot CH_2Br\\ |\\ CH_2\cdot CH_2\cdot COCH_3\end{array} \xrightarrow{NH_3} \begin{array}{l}CH_2\cdot CH_2\cdot NH\\ |\qquad\qquad\quad |\\ CH_2\cdot CH{=}C\cdot CH_3\end{array}$$

are reduced to the corresponding piperidines even by tin and hydrochloric acid and are very easily decomposed, *e.g.*, by treatment with benzoyl chloride and aqueous NaOH, to derivatives of δ-amino ketones. N-Alkylated and N-arylated 1,2,3,4-tetrahydropyridines decompose so readily that some, such as 1-phenyl-1,2,3,4-tetrahydropicoline, are stable only as salts. The 1,2,5,6-tetrahydro- and 1,2,3,4-tetrahydropyridines resemble the 1,4- and 2,3-dihydropyrroles (p. 47) in the divergence of their behavior.

3-Ethyl-1,2,5,6-tetrahydropyridine, b.p. 158°. **3-Ethyl-4-methyl-1,2,5,6-tetrahydropyridine,** b.p. 177°, and **2-methyl-5-ethyl-1,2,5,6-tetrahydropyridine,** from the corresponding pyridines with Na and alcohol.

1,2,3,4-**Tetrahydropicoline,** Δ^2-*pipecoleïne,* b.p. 132°, is reduced by tin and hydrochloric acid to pipecoline; it is decomposed by benzoyl chloride and aqueous NaOH to N-benzoyl-δ-acetylbutylamine and by nitrous acid to γ-acetylbutanol (*Lipp,* Ann. **289,** 173; *Gabriel,* Ber. **42,** 1242). 2-**Phenyl**-1,2,3,4-**tetrahydropyridine,** m.p. about 18°, b.p. 276°, from δ-aminovalerophenone (Vol. III, p. 406) (*Gabriel,* Ber. **41,** 2010). 2,3-**Dimethyl**-1,2,3,4-**tetrahydropyridine,** b.p. 155°. 1-**Methyl**-1,2,3,4-**tetrahydropicoline,** b.p. 146°, is converted by benzoyl chloride and aqueous sodium hydroxide to the N-benzoyl derivative, and by hydroxylamine and semicarbazide to the oxime and semicarbazone of N-methyl-δ-acetylbutylamine. This tendency of the 1,2,3,4-tetrahydropyridine ring to open explains the conversion of the 1-methyltetrahydropicoline to 1-methyl-3-acetylpiperidine with formaldehyde (*Lipp, Widnmann,* Ber. **38,** 2471):



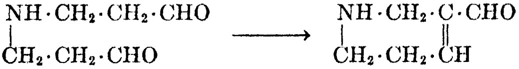
$$\begin{array}{l}CH_2\text{—}CH_2\text{—}CH\\ |\qquad\qquad\qquad \|\\ CH_2\cdot N(CH_3)\cdot C\cdot CH_3\end{array} \longrightarrow \begin{array}{l}CH_2\cdot CH_2\cdot CH_2\cdot COCH_3\\ |\\ CH_2\cdot NHCH_3\end{array} \longrightarrow$$

$$\begin{array}{l}CH_2\text{—}CH_2\text{—}CH\cdot COCH_3\\ |\qquad\qquad\quad |\\ CH_2\cdot NHCH_3\ CH_2OH\end{array} \longrightarrow \begin{array}{l}CH_2\text{—}CH_2\text{—}CH\cdot COCH_3\\ |\qquad\qquad\qquad |\\ CH_2\cdot N(CH_3)\cdot CH_2\end{array}$$

2-*n*-**Propyl**-1,2,3,4-**tetrahydropyridine** is known as **γ-coniceine.** For tetrahydropyridine from piperidine oxide (p. 221), see *Wolffenstein,* Ber. **25,** 2782. An isomeric tetrahydropyridine is prepared by fusion of piperidinesulfonic acid with KOH (*Paal, Hubaleck,* Ber. **34,** 2761). For a tetrahydropyridine from N-methylheptenylamine, see *Wallach,* Ber. **38,** 2803.

The N-alkyl derivatives of pyridones (p. 209) and pyridinediols or glutaconimides are *oxo derivatives* of *di-* and *tetrahydropyridines.* They have been described in the section on pyridols (p. 209).

1,2,5,6-**Tetrahydropyridine**-3-**carboxaldehydes** result from the hydrolysis of iminodipropionacetal and its N-alkyl derivatives by intramolecular condensation of the iminodipropionaldehydes first formed (*Wohl,* Ber. **38,** 4154; **40,** 4679):

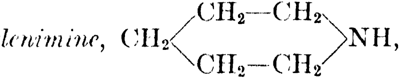


$$\begin{array}{l}NH\cdot CH_2\cdot CH_2\cdot CHO\\ |\\ CH_2\cdot CH_2\cdot CHO\end{array} \longrightarrow \begin{array}{l}NH\cdot CH_2\cdot C\cdot CHO\\ |\qquad\qquad\ \ \|\\ CH_2\cdot CH_2\cdot CH\end{array}$$

1,2,5,6-**Tetrahydropyridine**-3-**carboxaldehyde** exists only in the polymerized, amorphous form; hydrochloride, m.p. 145° (dec.); N-benzoyl derivative, m.p. 91°. Its oxime, m.p. 145°, loses water when treated with $SOCl_2$ to give the 3-

nitrile, b.p. 48° (0.2 mm.), from which cincholoiponic acid (p. **224**) is obtained by the addition of sodium malonic ester and subsequent saponification. **1-Methyl-1,2,5,6-tetrahydropyridine-3-carboxaldehyde**, b.p. 40–43° (0.17 mm.), with an amine-like odor. **1-Methyl-1,2,5,6-tetrahydropyridine-3-carbonitrile**, obtained through the oxime, yields the alkaloid *arecaidine* (p. 331) on saponification. **1-Ethyl-1,2,5,6-tetrahydropyridine-3-carboxaldehyde**, b.p. 53° (0.06 mm.).

(*c*) HEXAHYDROPYRIDINES, PIPERIDINES.

Hexahydropyridine, piperidine, *pentamethylenimine*,  $CH_2\left\langle\begin{matrix}CH_2-CH_2\\CH_2-CH_2\end{matrix}\right\rangle NH$, b.p. 106.2° (*Vorländer*, Ann. **345**, 277), is a liquid of characteristic odor. It is soluble in water and alcohol. It occurs bound to piperic acid as piperine in pepper; it is freed by heating piperine with alcoholic potash. It is synthesized: (*1*) by heating pentamethylenediamine hydrochloride (cadaverine); (*2*) by heating ε-chloro- and ε-bromoamylamine, as mentioned previously; and (*3*) by reduction of pyridine with Na and alcohol or nickel and H_2 (French Pat. 621434, 1926), or by catalytic reduction of pyridinium chloride with platinum oxide and H_2 in absolute ethyl alcohol solution (*Hamilton, Adams*, Am. **50**, 2260).

Piperidine is dehydrogenated to pyridine by heating with sulfuric acid at 300° or, better, with nitrobenzene at 260°, by boiling with silver oxide, silver acetate in glacial acetic acid, or by passing its vapor over MnO at 600° (*Sabatier, Gernandez*, C.r. **185**, 241).

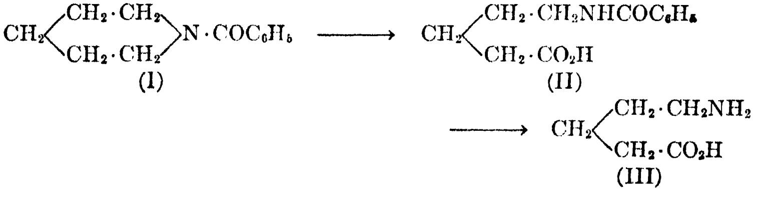
Since the discovery of their property of accelerating vulcanization [Ger. Pat. 265221, 1912; *Spence*, J.Soc.Chem.Ind. **36** (1917), 118], piperidine and many of its derivatives have been used in the rubber industry (U. S. Pats. 1463794, 1923; 1650975, 1927; Ger. Pat. 423101, 1920).

Decomposition of Piperidine.—The piperidine ring is ruptured in the following reactions:

1. When piperidine is heated with hydriodic acid at 300°, it decomposes into *n*-pentane and ammonia.

2. The unsubstituted piperidine is resistant to oxidizing agents, but does not possess unlimited stability. *Karrer* (Helv. **9**, 886) obtained *β-aminopropionic acid* from piperidine by long boiling with CrO_3; *γ-aminobutyric acid* had been produced earlier with HNO_3. For the oxidation of benzoylpiperidine to *δ-aminovaleric acid* with $KMnO_4$, see below. Piperidine itself is attacked by permanganate even in the cold, with lively evolution of ammonia (*Deléphine*, C.r. **184**, 206). For the products of oxidation with $KMnO_4$ in acetone, see *Goldschmidt, Voeth*, Ann. **435**, 265.

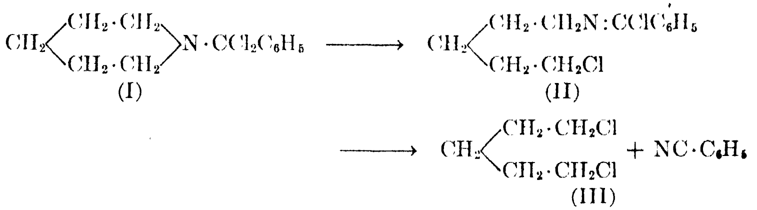
When benzoylpiperidine (I) is oxidized with potassium permanganate, δ-benzoylamino-*n*-valeric acid (II) is formed; with KOH this yields δ-amino-*n*-valeric acid (III) or homopiperidinic acid (*Schotten*, Ber. **17**, 2544). 1-Piperidinecarboxylic acid ethyl ester, piperidylurethan, on the other hand, is oxidized by nitric acid to carboxyethylaminobutyric acid, which gives γ-aminobutyric acid or piperidinic acid with KOH.



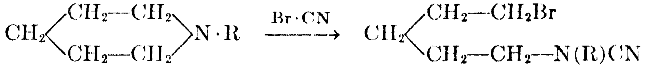
$$CH_2\left\langle\begin{matrix}CH_2\cdot CH_2\\CH_2\cdot CH_2\end{matrix}\right\rangle N\cdot COC_6H_5 \longrightarrow CH_2\left\langle\begin{matrix}CH_2\cdot CH_2NHCOC_6H_5\\CH_2\cdot CO_2H\end{matrix}\right. \longrightarrow CH_2\left\langle\begin{matrix}CH_2\cdot CH_2NH_2\\CH_2\cdot CO_2H\end{matrix}\right.$$

(I) (II) (III)

3. When benzoylpiperidine is heated with PCl_5, the dichlorobenzylpiperidine (I) first formed opens to N-ε-chloroamylbenzimide chloride (II), which decomposes further on distillation into 1,5-dichloropentane (III) and benzonitrile (*v. Braun*, Ber. **37**, 2915, 3210; *v. Braun, Sobecki*, Ber. **44**, 1039):

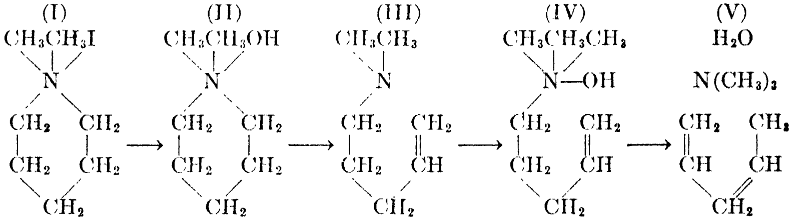


4. N-Alkyl- and N-arylpiperidines are split by cyanogen bromide to N-alkyl-N-cyano-ε-bromoamylamines (*v. Braun*, Ber. **40**, 3914):



The ease of decomposition depends on the alkyl group attached to the nitrogen (*v. Braun*, Ber. **42**, 2035).

With methyl iodide piperidine forms dimethyl piperidinium iodide (I), which is converted to the hydroxide (II) by moist silver oxide; the hydroxide decomposes on distillation into N,N-dimethyl-4-pentenylamine (III) (the so-called *des-base*) and water. The N,N-dimethyl-4-pentenylamine can be converted into 4-pentenyltrimethylammonium hydroxide (IV), which decomposes when distilled to give piperylene or 1,3-pentadiene (*Thiele*, Ann. **319**, 226) (V), trimethylamine, and water (*Hofmann, Ladenburg*, Ber. **16**, 2058; *v. Braun*, Ber. **42**, 2532; *cf.* the decomposition of the pyrrolidines, p. 48):



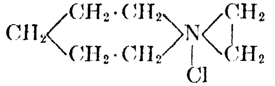
Piperidine Derivatives.—As an imine base, piperidine is capable of forming a nitroso compound, N-alkyl, and N-acyl derivatives. For the physiological action of piperidine derivatives, see *Wolffenstein, Wolffenstein*, Ber. **34**, 2408.

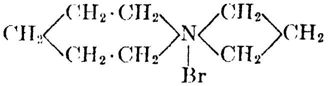
Nitrosopiperidine, $C_5H_{10}N\cdot NO$, b.p. 218°, from piperidine with nitrous acid, can be reduced to **N-aminopiperidine,** $C_5H_{10}N\cdot NH_2$, b.p. 146°, which yields dipiperidyl tetrazone, $(C_5H_{10}N)_2N_2$, m.p. 45°, when oxidized [*cf. Angeli, Castellana*, Atti accad.Lincei **14** (1905), I, 272]. For the electrolytic decomposition of nitroso piperidine and its homologues, see *Ahrens*, Ber. **31**, 2272; *Widera*, Ber. **31**, 2276.

1-Methylpiperidine, $C_5H_{10}NCH_3$, b.p. 107°; **1-ethyl-**, **1-propyl-**, and **1-isoamylpiperidine,** b.p. 128°, 149°, and 187°; **1-benzylpiperidine,** b.p. 245° (*Auerbach, Wolffenstein*, Ber. **32**, 2507); **1-allylpiperidine,** b.p. 152°. **1-Phenylpiperidine,** b.p. 258°, from 1,5-dibromopentane and aniline, is also obtained, rather surprisingly, when piperidine is heated with bromo- or iodobenzene (*Lellmann, Geller*, Ber. **21**, 1921; *Lellmann, Büttner*, Ber. **23**, 1388). 1-α- and **β-Naphthylpiperidine,** b.p. 215° (35 mm.) and m.p. 58°, from the naphthols with piperidine (*Roth*, Ber. **29**, 1175).

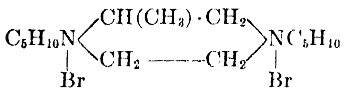
Hydrogen peroxide oxidizes piperidine to **piperidine oxide,** $C_5H_{10}NH:O$ or $C_5H_{10}N\cdot OH$, m.p. 39°, b.p. 110° (55 mm.). With phenylisocyanate this gives an O-phenylcarbamyl derivative, $C_5H_{10}N\cdot OCONHC_6H_5$, but with alkylating agents it yields N-alkylpiperidine oxides, which can also be obtained directly by oxidation of N-alkylpiperidines with H_2O_2 and which correspond to the dialkylaniline oxides (Vol. III, p. 83). **N-Methylpiperidine oxide,** $C_5H_{10}N(CH_3){:}O$; **N-propylpiperidine oxide,** m.p. 105°; **N-benzylpiperidine oxide,** m.p. 148°. When heated with acids they quickly lose oxygen, regenerating the piperidines. When heated alone the N-alkylpiperidine oxides decompose into piperidine oxide and olefines (*Haase, Wolffenstein*, Ber. **37**, 3228).

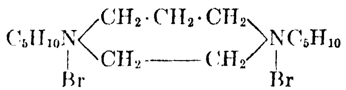
The isomeric bicyclic ammonium salts are formed when derivatives such as 1-β-chloroethyl- and 1-γ-bromopropylpiperidine are heated (*Scholtz, Friemehlt*, Ber. **32**, 850; *Pechmann, Hanke*, Ber. **34**, 357; *Gabriel, Colman*, Ber. **39**, 2875; **40**, 424; *v. Braun*, Ber. **39**, 4347; *Albert*, Ber. **42**, 545):





Similar compounds, which are significant in the *stereochemistry of nitrogen*, have been obtained from *s*-**dipiperidylethane,** $C_5H_{10}N \cdot CH_2CH_2 \cdot NC_5H_{10}$, m.p. 4°, b.p. 263°, by reaction with alkylene dibromides (*Aschan*, Ber. **32**, 988; *Scholtz*, Ber. **35**, 3047; *Löffler*, Ber. **37**, 161):





The product from dipiperidylethane and 1,3-dibromopropane and that from 1,3-dipiperidylpropane and *s*-dibromoethane are inactive stereoisomers (*cf. Scholtz*, Ber. **44**, 480):

N-Piperidineacetaldehyde, $C_5H_{10}N \cdot CH_2CHO$, m.p. 103° (*Stoermer*, Ber. **31**, 2541). **N-Piperidineacetone,** $C_5H_{10}N.CH_2COCH_3$ [*van Ark*, Arch.Pharm. **238** (1900), 330]. For N-piperidineacetic acid and homologues, see *Bischoff*, Ber. **31**, 2839; *Wedekind*, Ber. **32**, 722.

N-Acetylpiperidine, $C_5H_{10}NCOCH_3$, b.p. 226°. **N-Benzoylpiperidine,** C_5H_{10}-$NCOC_6H_5$, m.p. 48°, prepared by heating piperidine with benzoyl chloride in dry benzene, condenses with benzaldehyde when heated to form dibenzylpyridine (p. 205). **N-Piperidinecarboxylic acid ethyl ester,** *piperidylurethan*, $C_5H_{10}NCOO$-C_2H_5, b.p. 211° (*cf. Cazeneuve, Moreau*, C.r. **125**, 1107). The piperidine rings of N-benzoylpiperidine and N-carbethoxypiperidine are broken when these compounds are heated (see p. 221). **N-Piperidinecarboxamide,** *piperidylurea*, $C_5H_{10}NCONH_2$, m.p. 93° (*de la Roche*, Bull. **31**, 21). The piperidide of piperic acid is the alkaloid **piperine** (p. 332).

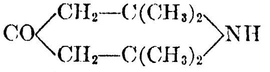
The *homologous piperidines* are prepared by reduction of the homologous pyridines with sodium and alcohol or of the 1,2,3,4-tetrahydropyridines with tin and hydrochloric acid (p. 219) or by synthetic methods (*Gunther*, Ber. **31**, 2134). They are: the **pipecolines,** $C_5H_9(CH_3)NH$; **lupetidines,** $C_5H_8(CH_3)_2NH$; **copellidines,** $C_5H_8(CH_3)(C_2H_5)NH$; *etc.* (*cf. Levy, Wolffenstein*, Ber. **28**, 2270).

The C-*alkylpiperidines* contain asymmetric C-atoms. Several of these bases have been separated by means of their bitartrates into optically active components; these include 2-**pipecoline** (*Marckwald*, Ber. **29**, 43; *Ladenburg*, Ber. **29**, 422), the **copellidine,** b.p. 163°, obtained from 2-methyl-5-ethylpyridine (p. 205) (*Levy, Wolffenstein*, Ber. **29**, 1959), 3-**propylpiperidine,** b.p. 174°, isomeric with coniine, which is synthesized from ε-chloro-β-propylamylamine (*Granger*, Ber. **30**, 1060), 2-**ethylpiperidine,** b.p. 143° (*Frese*, Ber. **33**, 3483; *Lipp*, Ber. **33**, 3513), and 3-**ethylpiperidine,** b.p. 155° (*Günther*, Ber. **31**, 2141). There is a remarkable increase in optical activity when alkyl groups are substituted on the nitrogen atom in 3-alkylpiperidines (*Hohenemser, Wolffenstein*, Ber. **32**, 2520; **34**, 2420). **2,6-Dimethylpiperidine,** *lupetidine*, is obtained in a *racemic* form (b.p. 133°), which can be resolved, and a *meso* form (b.p. 128°) (*Hohenemser, Wolffenstein*, Ber. **32**, 2520; *Marcuse, Wolffenstein*, Ber. **34**, 2426). Similar modifications are given by **2,6-diphenylpiperidine,** *racemic* form, liquid, *meso* form, m.p. 71°, while **2-phenyl-6-methylpiperidine** is formed in two stereoisomeric modifications, which are optically resolvable (*Scholtz, Müller*, Ber. **33**, 2842; *Scholtz*, Ber. **34**, 1616). **2,2,6,6-Tetramethylpiperidine,** b.p. 156° (see *Franchimont, Friedmann*, Rec. **24**, 404). Another interesting compound is the **3-ethyl-4-methyl-**

piperidine, since it is closely related to the degradation products of the quinuclidine half of quinine (p. 354).

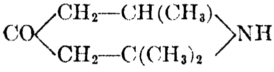
Oxo Derivatives of the Piperidine Series.—δ-Lactams are 2-oxopiperidines or 2-piperidones. **2-Piperidone,** b.p. 65° (0.4 mm.) (*Goldschmidt, Voeth,* Ann. **435,** 265).

The products of the reactions of phorone with ammonia and of diacetoneamine with acetaldehyde and with benzaldehyde are derivatives of 4-piperidone (*cf. Pauly,* Ber. **32,** 2244):



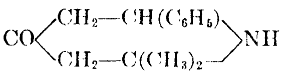
$$\mathrm{CO}\lt\begin{matrix}\mathrm{CH_2{-}C(CH_3)_2}\\ \mathrm{CH_2{-}C(CH_3)_2}\end{matrix}\gt\mathrm{NH}$$

2,2,6,6-Tetramethyl-4-piperidone
(*Triacetoneamine*)



$$\mathrm{CO}\lt\begin{matrix}\mathrm{CH_2{-}CH(CH_3)}\\ \mathrm{CH_2{-}C(CH_3)_2}\end{matrix}\gt\mathrm{NH}$$

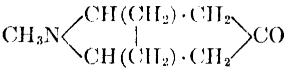
2,2,6-Trimethyl-4-piperidone
(*Vinyldiacetoneamine*)



$$\mathrm{CO}\lt\begin{matrix}\mathrm{CH_2{-}CH(C_6H_5)}\\ \mathrm{CH_2{-}C(CH_3)_2}\end{matrix}\gt\mathrm{NH}$$

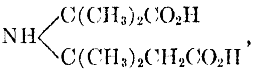
2,2-Dimethyl-6-phenyl-4-piperidone
(*Benzaldiacetoneamine*)

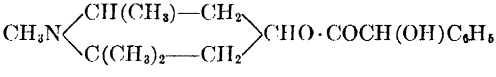
2,2,6,6-*Tetramethyl-4-piperidone* is of interest because of the similarity of its structure with tropine and tropinone (I):



$$\mathrm{CH_3N}\lt\begin{matrix}\mathrm{CH(CH_2)\cdot CH_2}\\ |\\ \mathrm{CH(CH_2)\cdot CH_2}\end{matrix}\gt\mathrm{CO}$$

(I)

(see atropine). It yields an acid,  $\mathrm{NH}\lt\begin{matrix}\mathrm{C(CH_3)_2CO_2H}\\ \mathrm{C(CH_3)_2CH_2CO_2H}\end{matrix}$, on oxidation, which is analogous to the oxidation of tropinone to tropinic acid (*Heintz,* Ann. **198, 74**). It reduces to **tetramethylhydroxypiperidine,** *triacetonealkamine,* $C_5H_6(CH_3)_4(OH)N$, which is converted to a tetrahydropyridine, **triacetonine,** by elimination of water. The tetramethylpiperidone reacts with bromine to form a **dibromo** derivative, which gives **tetramethylpyrrolinecarboxylic acid amide** (p. 48) with ammonia (*Pauly, Boehm,* Ber. **33,** 919). With mercaptans the tetramethylpiperidone forms **4-alkylthio-2,2,6,6-tetramethylpiperidines,** such as $C_5H_6(CH_3)_4(SC_2H_5)N$. 2,2,6-*Trimethyl-4-piperidone,* on the other hand, gives normal mercaptoles with mercaptans; these can be oxidized to sulfonals (*Pauly,* Ber. **31,** 3145). When **4-isonitroso-2,2,6-trimethylpiperidine,** m.p. 151°, is reduced, two stereoisomeric **4-aminotrimethylpiperidines,** $C_5H_7(CH_3)_3(NH_2)N$, are obtained: α-, m.p. 26°, b.p. 85° (22 mm.); β-, oil, b.p. 83° (22 mm.); with nitrous acid they give two stereoisomeric **trimethyl-4-piperidinols,** $C_5H_7(CH_3)_3(OH)N$, m.p. 137° and 161°, of which the latter is rearranged to the former by sodium amylate. The mandelic acid esters of the corresponding **tetramethyl-4-piperidinols:**



$$\mathrm{CH_3N}\lt\begin{matrix}\mathrm{CH(CH_3){-}CH_2}\\ \mathrm{C(CH_3)_2{-}CH_2}\end{matrix}\gt\mathrm{CHO\cdot COCH(OH)C_6H_5}$$

differ in their physiological properties, that from the stable isomer (oil) being ineffective while that from the labile isomer, m.p. 113°, is used as a *mydriatic* under the name **euphthalmine.**

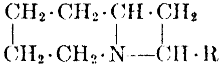
C-Piperidinesulfonic acid, $(C_5H_{10}N)SO_3H$, m.p. 188°, from piperidine and amidosulfonic acid at 180° (*Paal, Hubaleck,* Ber. **34,** 2757).

Reduction of pyridine alcohols (p. 211) with Na and alcohol gives *piperidine alcohols.* **2-Piperidineëthanol,** $C_5H_{10}N[2]CH_2CH_2OH$, m.p. 39°, b.p. 234°, from 2-pyridineëthanol (*picoline alkine,* p. **212**), is oxidized by CrO_3 to **2-piperidineacetic acid,** $C_5H_{10}N[2]CH_2COOH$, m.p. 214° (*Koenigs, Happe,* Ber. **36,** 2905). **1-Methyl-2-piperidineëthanol** is converted to 1-methyl-2-vinylpiperidine, b.p. 60° (12 mm.), by heating with hydrochloric acid (*Heidrich,* Ber. **34,** 1889).

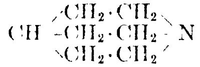
α-Methyl-2-piperidineëthanol, $C_5H_{10}N[2]CH_2CH(OH)CH_3$, m.p. 57°, b.p. 226–229°, loses water when treated with P_2O_5, yielding two stereoisomeric 2-

propenylpiperidines, $C_5H_{10}N[2]CH{:}CHCH_3$, m.p. 18°, b.p. 169°, and m.p. 15°, b.p. 167°, which can be resolved into optically active components by means of bitartrate (*Loffler*, *Friedrich*, Ber. **42**, 107). α-**Ethyl-2-piperidineëthanol**, C_5H_{10}-$N[2]CH_2CH(OH)C_2H_5$, m.p. 55°, b.p. 127° (15 mm.). The iodides obtained from the 2-piperidine alcohols with HI undergo an intramolecular alkylation when treated with alkali, forming bicyclic tertiary bases (I) which are called *conidines* (*Loffler*, *Plocker*, Ber. **40**, 1310; *Loffler*, *Remmler*, Ber. **43**, 2048). Similarly, the iodide (hydriodide, m.p. 191°) from **4-piperidineëthanol**, $C_5H_{10}N[4]CH_2$-CH_2OH, b.p. 141° (14 mm.), yields the bicyclic quinuclidine (II), m.p. 158°, which is significant because of its relation to the cinchona alkaloids (p. 351) (*Meisenheimer*, Ann. **420**, 190). **3-Ethylquinuclidine**, b.p. 191°, from 3-ethyl-4-piperidineëthanol, $C_5H_9N[3]C_2H_5[4]CH_2CH_2OH$, whose active form is obtained by reduction of cincholoiponic acid ester (p. 225) with Na and alcohol (*Koenigs*, *Bernhart*, Ber. **38**, 3049). α-**Ethyl-2-piperidinemethanol**, $C_5H_{10}N$-$[2]CH(OH)C_2H_5$, m.p. 99°, is the inactive form of *conhydrine* (p. 334); it is prepared by reduction of 2-propionylpyridine with sodium and amyl alcohol and is converted by further reduction into (*d* + *l*) coniine (p. 332). **2-Piperidinepropanol**, $C_5H_{10}N[2]CH_2CH_2CH_2OH$, b.p. 218°, is produced by reduction of 2-pyridineacrylic acid ester (p. 218) with Na and alcohol. With dehydrating agents such as concentrated H_2SO_4 or P_2O_5 it yields a little 2-allylpiperidine, $C_5H_{10}N$-$[2]CH_2CH{:}CH_2$, b.p. 171°, and much **piperolidine**, *octahydropyrrocoline* (III), b.p. 161°. The latter compound also results from the reduction of **piperolidone** (IV), b.p. 126° (12 mm.), the lactam of 2-piperidinepropionic acid, $C_5H_{10}N$-$[2]CH_2CH_2COOH$, m.p. 148°, which is obtained by reduction of 2-pyridineacrylic acid (*Löffler*, *Kaim*, Ber. **42**, 94; *Loffler*, *Flügel*, Ber. **42**, 3420).

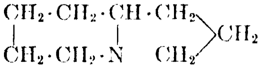
(I)



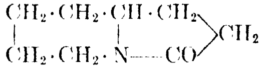
(II)



(III)



(IV)

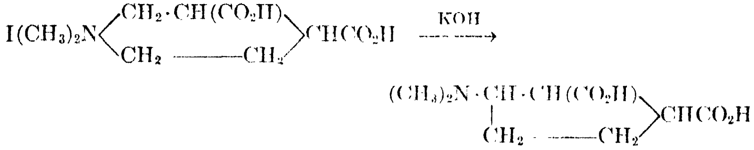


3-Piperidinecarboxaldehydes are prepared from the tetrahydropyridinecarboxaldehydes (p. 219) by conversion into 4-chloropiperidinecarboxaldehyde acetals with alcohol and hydrochloric acid followed by treatment with sodium and alcohol. **3-Piperidinecarboxaldehyde** itself, $(C_5H_{10}N\cdot CHO)_2$, is known only in bimolecular form; diethyl acetal, b.p. 55° (0.15 mm.) (*Wohl*, *Losanitsch*, Ber. **40**, 4695). **1-Ethylpiperidine-3-carboxaldehyde**, b.p. 44° (0.2 mm.), polymerizes even more readily (*Wohl*, *Losanitsch*, Ber. **38**, 4170).

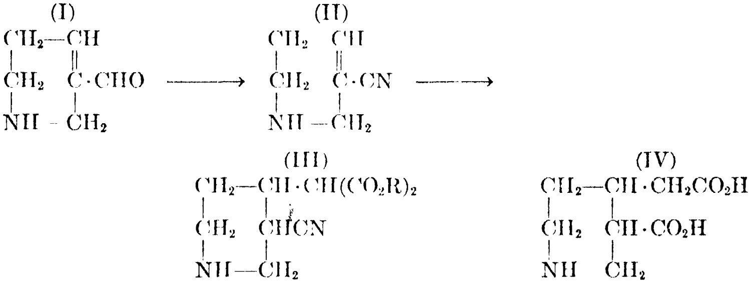
Pelletierine, one of the alkaloids of the pomegranate tree (p. 335) has been identified as *β-2-piperidinepropionaldehyde* (*Hess*, *Eichel*, Ber. **50**, 1192).

2,6-*Diphenacyl*-1-*methylpiperidine* occurs as **lobelanine**, $C_{22}H_{25}O_2$, an alkaloid closely related to the *lobeline* (p. 335) of the lobelia plant (*Wieland*, *Dragendorff*, Ann. **473**, 83; see under alkaloids).

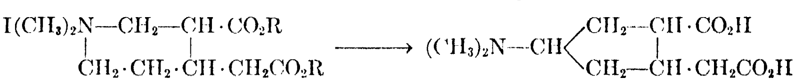
Piperidinecarboxylic acids are obtained by reduction of pyridinecarboxylic acids with sodium and alcohol. **Pipecolinic acid**, $C_5H_{10}N(COOH)$, m.p. 261°, has been resolved into *d*- and *l*-pipecolinic acid, m.p. 270°, by means of the bitartrate (*Mende*, Ber. **29**, 2887); the *l*-acid is also formed by the oxidation of conhydrine (*Willstätter*, Ber. **34**, 3166). **Hexahydroquinolinic acid**, $C_5H_9N(COOH)_2$, is similarly prepared from the hydrophthalic acids in two stereoisomeric modifications, m.p. 227° and 253°, each of which can be resolved into two optically active forms (*cf.* *Besthorn*, Ber. **29**, 2665). **Hexahydrocinchomeronic acid**, inactive *loiponic acid*, m.p. 256° (dec.), (*Koenigs*, *Wolff*, Ber. **29**, 2187), results from further oxidation and deactivation of cincholoiponic acid, a decomposition product of cinchonine (p. 351). The methyl iodide addition product of N-methylhexahydrocinchomeronic acid reacts to alkali somewhat differently than N,N-dimethylpiperidinium iodide (p. 221): it forms a dimethylaminocyclopentanedicarboxylic acid (*Skraup*, *Piccoli*, Mo. **23**, 269):



The homologous **cincholoiponic acid**, *3-carboxy-4-piperidineacetic acid*, m.p. 222° (anhydrous), is prepared similarly; it is an important decomposition product of the cinchona alkaloids, and is converted by further oxidation to *loiponic acid*. It has been synthesizd by *Wohl* (*Wohl, Losanitsch*, Ber. **40**, 4698; *Wohl, Maag*, Ber. **42**, 627). The synthesis starts from 1,2,5,6-tetrahydropyridine-3-carboxaldehyde (I) (p. **219**), produced by hydrolysis of iminodipropionaldehyde acetal; its oxime is converted by $SOCl_2$ to tetrahydropyridine-3-nitrile (II). The ester nitrile (III) obtained from this nitrile by addition of sodium malonic ester yields on saponification with barium hydroxide solution *rac*-cincholoiponic acid (IV) in two stereoisomeric forms; the higher-melting modification, when resolved by means of brucine, gives a *d*-cincholoiponic acid identical with a decomposition product of the cinchona alkaloids:

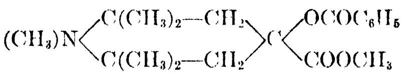


The methyl iodide addition product of cincholoiponic acid is rearranged by alkali in a manner similar to the hexahydrocinchomeronic acid, dimethylaminocarboxycyclopropaneacetic acid being formed (*Skraup*, Mo. **21**, 879):



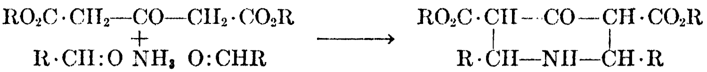
2,6-**Piperidinedicarboxylic acid**, from dibromopimelic acid with ammonia (*Fischer*, Ber. **34**, 2543).

Eucaine, 1,2,2,6,6-pentamethyl-4-benzoyloxypiperidine-4-carboxylic acid ester:



has been recommended as an anesthetic to substitute for cocaine (*Merling*, Ber. **6**, 173; *Parsons*, Am. **23**, 885).

A large number of 4-**piperidone-3,5-dicarboxylic acid esters** have been prepared by condensation of β-ketoglutaric acid ester with aldehydes and NH_3 or primary amines (*Petrenko-Kritschenko*, J.pr. **85**, 1):

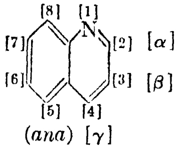


Other piperidine derivatives which are alkaloids or decomposition products of alkaloids, such as coniine or 2-propylpiperidine, tropine, and ecgonine, are treated in the section on alkaloids.

(b) Quinoline Group

The bases of the quinoline or 2,3-benzopyridine group occur together with those of the pyridine group in bone oil and coal tar. They are also obtained from various alkaloids by distillation with potassium hydroxide; quinoline was first prepared by *Gerhardt* in 1842 in this way from the alkaloid cinchonine.

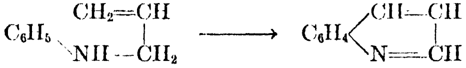
Its manner of synthesis, mode of reaction and number of isometric derivatives indicate that quinoline has the following formula, which is similar to that of naphthalene except for the replacement of an α-CH group by N:



(For the arrangement of the double bonds, see *Auwers*, Z.physikal.Chem. **116**, 438.)

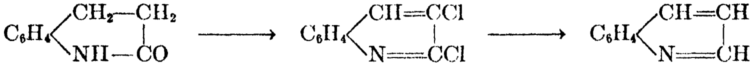
Substituents in the pyridine ring, which were designated α, β, γ in the old nomenclature, are now numbered 2, 3, and 4, respectively, N being considered position 1; the numbers 5, 6, 7, and 8 indicate substituents in the benzene ring. The older method used the symbols *o*, *m*, and *p* for substituents in the 8, 7, and 6 positions, respectively. Substituents in the benzene ring were often indicated by the symbol *Bz*, and those in the pyridine ring by *Py*.

The constitution of quinoline was first disclosed by its synthesis by *Königs* from allylaniline over lead oxide heated to redness (this is analogous to the formation of naphthalene from phenylbutylene):



$$C_6H_5\begin{matrix}CH_2{=}CH\\ |\\ NH{-}CH_2\end{matrix} \longrightarrow C_6H_4\begin{matrix}CH{-}CH\\ |\\ N{=}CH\end{matrix}$$

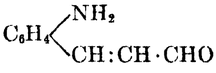
A more direct proof of its constitution is offered by its preparation from hydrocarbostyril (p. 245); the latter is treated with PCl_5 to give a dichloride which is reduced with hydriodic acid (*Baeyer*, Ber. **12**, 1320):



$$C_6H_4\begin{matrix}CH_2{-}CH_2\\ |\\ NH{-}CO\end{matrix} \longrightarrow C_6H_4\begin{matrix}CH{=}CCl\\ |\\ N{=}CCl\end{matrix} \longrightarrow C_6H_4\begin{matrix}CH{=}CH\\ |\\ N{=}CH\end{matrix}$$

Methods of Formation of Quinoline Derivatives.—(*1*) Condensation of *o*-amino compounds of benzene derivatives which have an oxygen atom attached to the third carbon atom of a side chain.

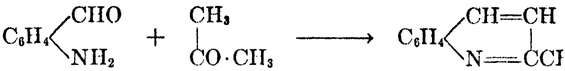
For example, quinoline is formed from *o-aminocinnamaldehyde*,



$$C_6H_4\begin{matrix}NH_2\\ CH{:}CH{\cdot}CHO\end{matrix}$$

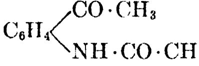
2-methylquinoline from *o-aminostyryl methyl ketone*, and 2-hydroxyquinoline (carbostyril) from *o-aminocinnamic acid*.

(*2*) Condensation of *o*-aminobenzaldehyde or *o*-aminobenzyl ketones with compounds containing the grouping $—CH_2CO—$, such as aldehydes, ketones, acetoacetic esters, and malonic acid esters in the presence of sodium hydroxide (*Friedländer*, Ber. **16**, 1833; **25**, 1752):



$$C_6H_4\begin{array}{l}\diagup CHO\\ \diagdown NH_2\end{array} + \begin{array}{l}CH_3\\ |\\ CO\cdot CH_3\end{array} \longrightarrow C_6H_4\begin{array}{l}\diagup CH{=}CH\\ \qquad\quad\;\; |\\ \diagdown N{=}CCH_3\end{array}$$

The *o*-amino compounds used as starting materials in method *1* are formed as an intermediate stage in this synthesis.

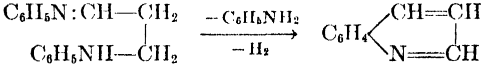
In this way cinchoninic acid and derivatives of it are formed from isatinic acid and aldehydes (*Pfitzinger*, J.pr. **66**, 263), 4-quinolinols from anthranilic acid and aldehydes or ketones, and 2-quinolinols from *o*-acylaminoacetophenones, such as  $C_6H_4\begin{array}{l}\diagup CO\cdot CH_3\\ \diagdown NH\cdot CO\cdot CH_3\end{array}$ [*Camps*, Ber. **32**, 3228; Arch.Pharm. **237** (1900), 426].

The synthesis of quinoline from *o*-toluidine and glyoxal and that of 3-hydroxyquinaldine from *o*-toluidine and pyruvic acid are similar (*Pulvermacher*, Ber. **27**, 628; *Kulisch*, Mo. **16**, 351).

(*3*) The *Skraup* synthesis. Quinoline and its derivatives substituted in the benzene nucleus are prepared from aniline and other primary aromatic amines by heating with glycerol and sulfuric acid at 140° in the presence of nitrobenzene or arsenic acid as an oxidizing agent (*Knueppel*, Ber. **29**, 703):

$$C_6H_5NH_2 + C_3H_8O_3 \longrightarrow \underset{\text{Quinoline}}{C_9H_7N} + 3\,H_2O + 2\,H$$

Probably acrolein is first formed from the glycerol; this reacts with aniline to give the anil of *β*-anilinopropionaldehyde, which splits off aniline and two hydrogen atoms to yield quinoline (*Blaise*, *Marie*, Bull. [4] **3**, 667):



$$\begin{array}{r}C_6H_5N{:}CH{-}CH_2\\ |\;\;\\ C_6H_5NH{-}CH_2\end{array} \xrightarrow[-H_2]{-C_6H_5NH_2} C_6H_4\begin{array}{l}\diagup CH{=}CH\\ \qquad\quad\;\; |\\ \diagdown N{=}CH\end{array}$$

This interpretation of the course of the reaction is confirmed experimentally by the immediate conversion of the anil of *β*-anilinoacrolein (from 2-propynylacetal and aniline: *Claisen*, Ber. **36**, 3667) into quinoline on fusion with zinc chloride (*König*, Ber. **56**, 1853).

Halogen, nitro, hydroxy, and methyl derivatives of aniline react in the same way as aniline. Diaminobenzenes give phenanthrolines (p. 265) and naphthylamines, naphthoquinolines (p. 248). Instead of a mixture of aromatic amine with nitrobenzene, the corresponding nitro compound can be used alone; this is partially reduced to the amine by the hydrogen released in the reaction. The first synthesis of this type was the preparation of alizarin blue (p. 248) from nitroalizarin (Vol. III, p. 663), glycerol, and sulfuric acid (*Graebe*, Ann. **201**, 333). Phenylhydroxylamine can be used in place of aniline in the *Skraup* synthesis (*Bamberger*, *Weetnauer*, Ber. **55**, 3376).

(*4*) The following methods can be considered as modifications of the *Skraup* synthesis:

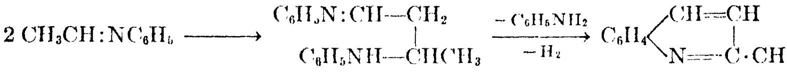
(*a*) *The quinaldine synthesis of Döbner and Miller.*—Quinolines substituted in the benzene or in the pyridine ring are obtained by condensation of anilines with aldehydes in the presence of sulfuric or hydrochloric acid. Quinaldine (2-methylquinoline) is formed from aniline and acetaldehyde:

$$C_6H_5NH_2 + 2\,CH_3CHO \longrightarrow \underset{\text{Quinaldine}}{C_9H_6N(CH_3)} + 2\,H_2O + 2\,H$$

Any aldehyde of the formula $R\cdot CH_2\cdot CHO$ can be used in the reaction. It condenses with itself to give the unsaturated aldehyde,

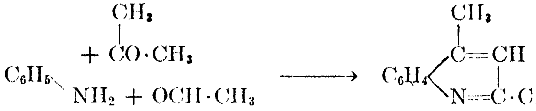
$R\cdot CH_2\cdot CH{:}CR\cdot CHO$, which reacts with the aniline to form 2-alkylquinolines.

Apparently the alkenylaniline first formed is converted into an aldol-like dimolecular condensation product, which loses aniline to give quinaldine (*Bischler*, Ber. **25**, 2864; *v. Miller, Plöchl*, Ber. **29**, 59):

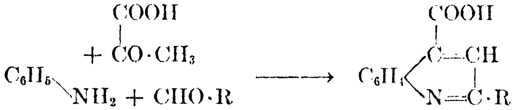


The hydrogen evolved in the reaction sometimes causes a partial reduction of the reaction product to a tetrahydroquinoline derivative (p. 244).

(*b*) A mixture of two aldehydes or of an aldehyde and a ketone can be used in place of one aldehyde. The product is a 2,4-di- or a 2,3,4-trialkylquinoline (*Beyer*, Ber. **20**, 1908). For example:

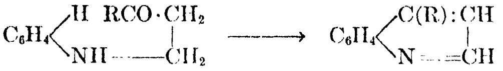


(*c*) A mixture of an aldehyde with pyruvic acid condenses with aniline to give a *2-alkylcinchoninic acid* (2-alkylquinoline-4-carboxylic acid) (p. 241) (*Dobner, Fettback*, Ann. **281**, 1; *Borsche*, Ber. **42**, 4072; for the course of the reaction, see *Bodforss*, Ann. **455**, 41):

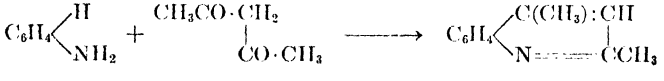


This reaction runs so smoothly, particularly when β-naphthylamine is used in place of aniline, that the formation of a naphthocinchoninic acid may be used for the *detection of aldehydes* or of *pyruvic acid* (Vol. I, p. 463) *in mixtures*. Pyruvic acid alone also condenses with aniline, since part of it is first converted into aldehyde; the products are 2-methylcinchoninic acid (aniluvitoninic acid) and phenyllutidone.

(*d*) β-Chloroethyl ketones, such as $CH_2ClCH_2COCH_3$, when heated with aniline and aniline hydrochloride in the presence of alcohol yield 4-alkylquinolines. β-Anilinoethyl ketones are formed as intermediate products and condense in this way (*Blaise, Maire*, Bull. [4] **3**, 667):



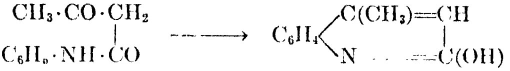
(*e*) β-Diketones with anilines and dehydrating agents form quinolines (*cf. Bülow, Issler*, Ber. **36**, 2448; **36**, 4013; *Roberts, Turner*, J. **1927**, 1832):



o,p-Directing substituents in the meta position to the N favor the ring closure but in the para position hinder it (*Roberts, Turner*, J. **1927**, 1832).

(*5*) Hydroxyquinoline derivatives are obtained by ring closure of aniline derivatives of β-ketonic acids and β-dicarboxylic acids:

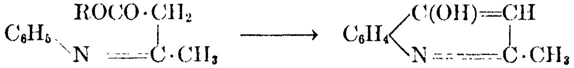
(*a*) Acetoacetanilide (from aniline and acetoacetic ester at 110°) is condensed by concentrated acids to 4-methylcarbostyril (4-methylquinolinol-2) (*Knorr*, Ann. **236**, 112):



Acetoacetic acid anilide 4-Methylquinolinol-2

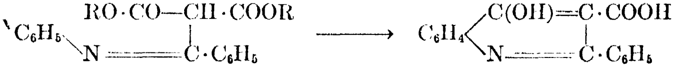
α-Acetopropionic acid anilide by the same treatment yields 3,4-dimethylcarbostyril; acetoacetic acid methyl anilide gives the N-methyl derivative of 4-methylpseudocarbostyril (p. 238).

(*b*) Acetoacetic ester anil (or the tautomeric β-anilinocrotonic acid ester), prepared from acetoacetic ester and aniline at room temperature, forms, when heated at 250°, 2-methylquinolinol-4 (*Conrad, Limpach*, Ber. **24**, 2990):



Acetoacetic ester anil 2-Methylquinolinol-4

Benzoyl acetic acid ester, acetonedicarboxylic acid ester, and the like react similarly. Homologues of aniline, antivanillic acid, or phenylenediamine can be used in place of aniline (*Bywanck*, Ber. **31**, 2143; *Besthorn, Garben*, Ber. **33**, 3439, 3448; *v. Niementowski*, Ber. **38**, 2044). Benzanilide imide chloride and sodium malonic acid ester form the anil of benzoylmalonic acid ester, which condenses to 4-hydroxy-2-phenylquinoline-3-carboxylic acid ester (*Just*, Ber. **19**, 1541):



Phosphorus pentachloride converts N-phenylmalonamic acid into 2,3,4-*trichloroquinoline* (*Rugheimer*, Ber. **18**, 2975; *Rugheimer, Schramm*, Ber. **20**, 1235). The alkylmalonanilic acids condense in the same way.

(*6*) The conversion of *indoles* to 3-chloro- or 3-bromoquinoline derivatives (p. 235), analogous to that of pyrroles to pyridines, is accomplished by heating them with sodium alcoholate and $CHCl_3$ or $CHBr_3$. α-Methylindole rearranges to quinoline when its vapors are led through a glowing tube (*Pictet*, Ber. **38**, 1949).

(*7*) A mixture of aniline with acetaldehyde vapors over hot aluminum oxide yields 4-methylquinoline (lepidine) and a little 2-methylquinoline (quinaldine) (*Tschitschibabin, Oparina*, Ber. **60**, 1873). In the condensation of *acetylene* with ammonia at high temperatures a small quantity of quinoline is found among the products (*Meyer, Wesche*, Ber. **50**, 424).

Quinoline and many of its alkyl homologues occur in coal tar, lignite tar [*Frank, Vollmer*, Braunkohle **23** (1924), 505], and low-temperature tar.

Properties of Quinolines.—The quinoline bases are liquids with a pungent odor; they are sparingly soluble in water and readily soluble in alcohol and ether. They are tertiary bases and resemble the pyridines in these chemical properties:

1. They form *salts and double salts* (which are described under the individual compounds).

2. With alkyl iodides, dialkyl sulfates, acid chlorides, chloroacetic acid, and the like they form *quinolinium* compounds (*Decker*, Ber. **38**, 1144; Eckstein, Ber. **39**, 2135). The ease of addition of alkyl iodides depends on the nature of the substituents in the quinoline compound (*Decker*, Ber. **24**, 1984). The quinoline iodoalkylates partially decompose on heating into quinoline and alkyl iodide. For their behavior with alkali see p. 230. With acid chlorides unstable addition compounds are generally formed.

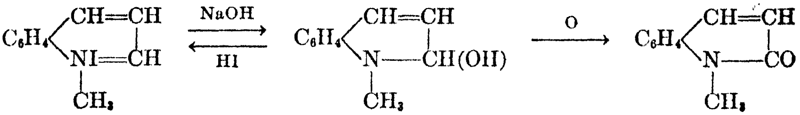
3. Quinoline, like pyridine, is but slightly attacked by nitric acid or chromic acid. Potassium permanganate, however, destroys the benzene ring, leaving 2,3-*pyridinedicarboxylic acid* (quinolinic acid) (p. 215). The homologous quinolines alkylated in either the pyridine or the benzene ring are oxidized by chromic acid in sulfuric acid solution to the corresponding *quinolinecarboxylic acids.* In the reaction of alkylated quinolines with potassium permanganate, the benzene ring is destroyed and *pyridinepolycarboxylic acids* are formed (*v. Miller,* Ber. **23,** 2252).

Potassium permanganate breaks down the pyridine ring of 2-alkylquinolines, leaving acid derivatives of *o*-aminobenzoic acid. Thus, 2-phenylquinoline gives *benzoylanthranilic acid* (*Doebner, Miller,* Ber. **19,** 1196). Also in the oxidation of quinolinium compounds the pyridine ring is ruptured; N-alkylquinolines are formed as intermediate products (see below).

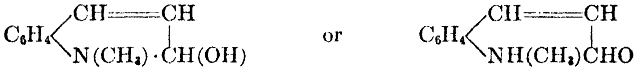
4. When reduced with zinc and hydrochloric acid or catalytically with hydrogen over finely divided nickel at 160–180°, the pyridine ring of quinoline compounds takes up four atoms of hydrogen to form tetrahydroquinolines (see p. 244). Energetic reduction produces decahydroquinolines.

QUINOLINE, b.p. 239°, m.p. −22.6°, d^{20} 1.095 (ebullioscopic constant = 56.1), is a colorless, pungent, highly refractive liquid with a powerful antiseptic action. It occurs in bone oil and coal tar. It is obtained from various alkaloids and is prepared synthetically, according to *Skraup's* method, by boiling a mixture of glycerol, aniline, sulfuric acid, and nitrobenzene or arsenic acid several hours (*Skraup,* Mo. **2,** 139; *Walter,* J.pr. **49,** 549; *Knueppel,* Ber. **29,** 704). It forms crystalline salts with one equivalent of acid; the dichromate, $(C_9H_7N)_2H_2Cr_2O_7$, m.p. 165°, is sparingly soluble and can be used for the purification of quinoline. The numerous molecular compounds with metal salts are also suitable for this purpose, *e.g.,* the chloroplatinate, $(C_9H_8N)_2PtCl_6 + 2\,H_2O$, m.p. 218°; picrate m.p. 203°. For the production of pure quinoline from crude coal tar quinoline by heating with copper oxide, see Ger. Pat. 451590, 1925; Frdl. **XV,** 340. *Quinoline betaine,* $C_9H_7\overbracket{N\cdot CH_2\cdot CO\cdot O}$, m.p. 171°, from quinoline and chloroacetic acid in the form of its hydrochloride [*Ihlder,* Arch.Pharm. **240** (1902), 504; *Decker, Kopp,* Ber. **39,** 72]. *Quinoline-N-oxide* (hydrate), m.p. 62°; picrate, m.p. 143°; from quinoline and perbenzoic acid (*Meisenheimer,* Ber. **59,** 1848). Reduction of quinoline gives *di-, tetra-, hexa-,* and *decahydroquinoline* (p. 243).

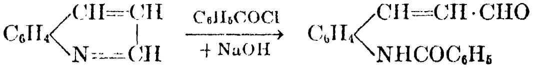
Alkylquinolinium compounds.—**1-Methylquinolinium iodide,** $C_9H_7N\cdot CH_3I + H_2O$, m.p. 72° (anhydrous, m.p. 133°). **1-Ethylquinolinium iodide,** m.p. 159°. Like the pyridinium hydroxides, the water-soluble hydroxides first formed by the action of alkali on quinoline alkyl iodides are unstable (with the exception of the amino- and hydroxyquinolinium bases), and rearrange into the nonconducting dihydro-2-quinolinols (pseudo-bases, quinolanols), which are insoluble in water. The latter are quite reactive, and are simultaneously oxidized and reduced by sodium hydroxide to N-alkyl-2-quinolones and N-alkyltetrahydroquinolines. With alkaline potassium ferricyanide solution only the N-alkyl-2-quinolone is formed (*Roser,* Ann. **282,** 363; *Decker,* Ber. **36,** 2568). With acids the pseudo-bases change back to the original quinolinium salts:



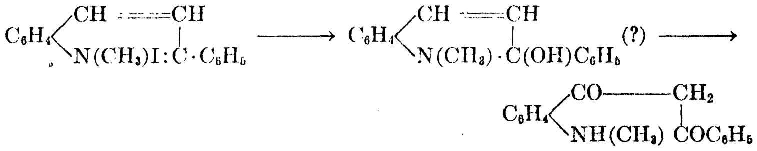
The hydroxyl group of the dihydro-2-quinolinols is very active. When these compounds are boiled with alcohol they are converted to alkoxy compounds or alcoholates. They react with aniline, phenylhydrazine, hydroxylamine, and compounds containing an activated methylene group, splitting off water (*Kaufmann, Strübin*, Ber. **44**, 680; *Decker, Kaufmann*, J.pr. **84**, 219). In view of these reactions it has been considered possible that these compounds are not dihydro-2-quinolinols but the *o*-alkylaminocinnamaldehydes formed by an opening of the ring similar to that which has been observed in the case of dinitrophenylpyridinium chloride (p. 202):



Such a rupture of the quinoline ring is known to occur in several cases. *o*-Benzoylaminocinnamaldehyde is formed when quinoline is treated with benzoyl chloride and aqueous sodium hydroxide (*Reissert*, Ber. **38**, 3415):



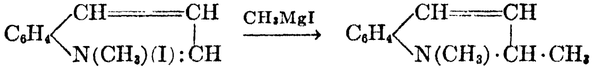
1-Methyl-2-phenylquinolinium iodide is converted by aqueous sodium hydroxide to a very reactive hydroxydihydroquinoline, which is oxidized even by the oxygen of the air to *o*-methylaminodibenzoylmethane (*Kaufmann, Janini*, Ber. **44**, 2670):



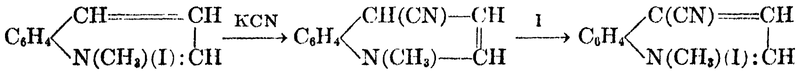
The great reactivity of the hydroxydihydroquinolines and their dehydrogenation products, the quinolones, and the ease of condensation of 2- and 4-methylquinolines (p. 232) make possible the formation of the valuable blue and red dyes of the *cyanine*, *isocyanine*, and *apocyanine* groups (see p. 235).

The following reactions of the 1-alkylquinolinium halides are similar to the rearrangement of quinolinium hydroxides to dihydroquinolinols:

(*a*) With alkylmagnesium halides they yield 1,2-dialkyldihydroquinolines (*Freund, Richard*, Ber. **42**, 1101; *Meisenheimer, Stotz, Bauer*, Ber. **58**, 2320):



(*b*) With potassium cyanide very reactive N-alkyldihydrocinchoninic acid nitriles are formed, probably by rearrangement of quinolinium cyanides, the first products; they are converted by oxidation with potassium ferricyanide into 1-alkyl-4-cyano-2-quinolones and by treatment with iodine solution into 1-alkyl-4-cyanoquinolinium iodides (*Kaufmann, Widmer*, Ber. **44**, 2058):



With benzoyl chloride and potassium cyanide they react in an unexpected manner, forming 1-benzoyldihydroquinaldinic acid nitrile (*Reissert*, Ber. **38**, 1606). For the action of cyanogen bromide on quinoline, see *Shimidzui*, J. Pharm.Soc.Japan **1926**, No. 529, 25; of chloroformic acid ester, see *Hopkins*, J. **117**, 278.

HOMOLOGOUS QUINOLINES. (For the numbering of the quinoline ring, see the formula on p. 226.) All seven isomeric methylquinolines are known. The four quinolines methylated in the benzene nucleus are called toluquinolines or methylbenzoquinolines; they are produced by the application of the *Skraup* reaction to the three toluidines. 8(or *o*)-**Methylquinoline**, b.p. 248°; 6(or *p*)-**methylquinoline**, b.p. 257°; 7(or *m*)-**methylquinoline**, b.p. 248°; **5-methylquinoline**, b.p. 250°.

QUINALDINE, 2(or *α*)-**methylquinoline**, b.p. 247°, is present in coal tar quinoline (up to 25%) (*Jacobsen*, *Reimer*, Ber. **16**, 1082). It is prepared by the various synthetic methods given on p. **227** and also by reduction of 4-quinolinol (p. **239**) and by fusion of N-ethylacetanilide with zinc chloride (*Pictet*, *Fert*, Ber. **23**, 1903). It is obtained according to the method of *Döbner* and *v. Miller* by many hours' boiling of aniline with paraldehyde and crude hydrochloric acid (*Döbner*, *v. Miller*, Ber. **16**, 2465). Dichromate, m.p. 110°. 1-*Methylquinaldinium iodide*, m.p. 190°. N-*Oxide*, picrate, m.p. 174° (*Meisenheimer*, *Stotz*, Ber. **58**, 2334). Treatment with chlorine or bromine in the presence of sodium acetate gives 2-(trichloro- or tribromomethyl)-quinoline, m.p. 56° and 128°, both of which hydrolyze quantitatively to quinaldinic acid (*Hammick*, J. **123**, 2882).

3(or *β*)-**Methylquinoline**, m.p. 10-14°, b.p. 253°, is formed by heating *o*-aminobenzaldehyde with propionaldehyde at 220° (*Wislicenus*, *Elvert*, Ber. **42**, 1144).

LEPIDINE, 4(or *γ*)-**methylquinoline**, m.p. 257°, occurs together with quinoline in coal tar; it is prepared from cinchonine by distillation with KOH as well as by synthetic methods (*cf. Bywanck*, Ber. **31**, 2153). Lepidine is formed when a mixture of aniline with 2 molar proportions of acetaldehyde is passed over heated Al_2O_3 (*Tschitschibabin*, *Oparina*, Ber. **60**, 1873).

Chromic acid oxidizes all three methylquinolines to the corresponding quinolinecarboxylic acids (p. **241**); $KMnO_4$ gives pyridinetricarboxylic acids (p. **216**).

2,3-Dimethylquinoline, b.p. 261° (*Rohde*, Ber. *22*, *267*); **2,4-dimethylquinoline**, b.p. 266°, from acetylacetone and aniline. **3,4-Dimethylquinoline**, m.p. 65°, b.p. 290°, from 3,4-dimethylcarbostyril.

2,8-Dimethylquinoline (*o-toluquinaldine*), m.p. 27° (*Wyler*, Ber. **60**, 298).

2-Ethylquinoline, b.p. 255-260°, and **3-ethylquinoline**, b.p. 265°, are formed when ethylquinolinium iodide is heated to 250° (analogous to preparation of alkylpyridines, p. 204). **4-Ethylquinoline**, b.p. 270-275°. **4-Propylquinoline**, b.p. 159° (16 mm.). For **trimethylquinolines**, see *Yamaguchi*, J.Pharm.Soc. Japan **1924**, 5. **2-Phenethylquinoline**, see p. 233.

Tetramethylquinolines: 2,4,5,7-, m.p. 59°; 2,4,6,8-, m.p. 86°; 2,4,5,8-, m.p. 131° (*Mikeska*, *Adams*, Am. **42**, 2394).

As in the case of the 2- and 4-methylpyridines (p. 204), the 2- and 4-CH_3 or -CH_2R groups in the quinoline series condense with aldehydes and also react with nitrosobenzene and nitrosodimethylaniline [*Browning*, *Cohen*, *Ellingworth*, *Gulbransen*, Proc.Roy.Soc.London B **100** (1926), 293]. The 2-methyl groups also condense with phthalic anhydride.

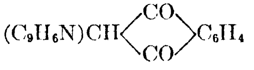
Formaldehyde and quinaldine give **2-quinolineëthanol**, *methylolquinaldine*, $C_9H_6N[2]CH_2CH_2OH$, m.p. 105°, *β*-**hydroxymethyl-2-quinolineëthanol**, *dimethylolquinaldine*, $C_9H_6N[2]CH(CH_2OH)_2$, m.p. 117°, and *β*,*β*-**di-(hydroxymethyl)-2-quinolineëthanol**, *trimethylolquinaldine*, $C_9H_6N[2]C(CH_2OH)_3$, m.p. 143°. If the 3-position is substituted, the 2-methyl group condenses with just two molecules of formaldehyde: *β*-**hydroxymethyl-3-methyl-2-quinolineëthanol**, *3-methyl-2-dimethylolquinaldine*, $C_9H_5N[3]CH_3[2]CH(CH_2OH)_2$, m.p. 107°. Similarly, lepidine gives only 4-**quinolineëthanol**, *methylollepidine*, $C_9H_6N[4]CH_2CH_2OH$, oil, and *β*-**hydroxymethyl-4-quinolineëthanol**, *dimethylollepidine*, $C_9H_6N[4]CH(CH_2OH)_2$, m.p. 128°. In 2,4-dimethylquinoline the 2-methyl group reacts first: **4-methyl-2-quinolineëthanol**, m.p. 98°, and *β*-**hydroxymethyl-4-methyl-2-quinolineëthanol**, m.p. 140°. Chloral and phthalic anhydride also react with 2-methyl groups (*Koenigs*, *Mengel*, Ber. **37**, 1322; see next page).

By elimination of water, quinolineëthanol yields 2-vinylquinoline, $C_9H_6N[2]CH{:}CH_2$; the *β*-hydroxymethylquinolineëthanols are reduced by hydriodic acid to **2- and 4-isopropylquinoline** (*Koenigs*, Ber. **32**, 223).

Depending on the reaction conditions, quinaldine and lepidine condense with benzaldehyde to give either 2- and 4-**styrylquinoline** (*benzylidenequinaldine* and *benzylidenelepidine*), m.p. 100° and 92°, or **benzylidenediquinaldine** and **benzylidenedilepidine**, $(C_9H_6N \cdot CH_2)_2CHC_6H_5$, m.p. 156° (dec.) and 218°. 2-Styrylquinolines with certain substituents (halogen, alkoxy, hydrazino, *etc.*) in the 4-position have strong bactericidal properties [*Browning*, *Cohen*, *Ellingworth*, *Gulbransen*, Proc.Roy.Soc.London B **100** (1926), 293; Ger. Pat. 440008, 1924]. Reduction of 2- and 4-styrylquinoline yields 2- and 4-phenethylquinoline, m.p. 30° and 101°, which can also be condensed with 1 or 2 molar proportions of formaldehyde (*Koenigs*, Ber. **32**, 3599).

Lepidine condenses with chloral to give α-**(trichloromethyl)-4-quinolineëthanol**, $(C_9H_6N)CH_2CH(OH)CCl_3$, m.p. 175°. The analogous 2-**derivative**, m.p. 144°, obtained very easily from quinaldine and chloral, is hydrolyzed by alkali to 2-quinolinelactic acid, $(C_9H_6N)CH_2CH(OH)COOH$, and 2-quinolineacrylic acid, $(C_9H_6N)CH{:}CHCOOH$; the quinolinelactic acid is converted by concentrated sulfuric acid to 2-quinolineacetaldehyde, $(C_9H_6N)CH_2CHO$, m.p. 104°, and by oxidation to 2-quinolineacetic acid, $(C_9H_6N)CH_2COOH$, m.p. 275°. The α-(trichloromethyl)-4-quinolineëthanol is hydrolyzed to 4-**quinolineacrylic acid,** m.p. 250–255° (dec.), which is reduced by HI and phosphorus to 4-**quinolinepropionic acid**, m.p. 203° (*Koenigs*, *Müller*, Ber. **37**, 1337).

When heated with phthalic anhydride at 220°, quinaldine forms a yellow dye, **quinophthalone**:



$$(C_9H_6N)CH\langle\begin{matrix}CO\\CO\end{matrix}\rangle C_6H_4$$

m.p. 241°; at lower temperatures the reaction product is the isomeric 2-**quinolinemethylenephthalide**, *isoquinophthalone*, $(C_9H_6N)CH{:}\overline{C\cdot C_6H_4COO}$, m.p. 187°, which rearranges to quinophthalone when heated to 250° or when treated with sodium ethylate (*Eibner*, *Merkel*, Ber. **37**, 3006). This reaction is comparable to the conversion of benzylidenephthalide to phenyldiketohydrindene. *Quinoline yellow*, a silk and wool dye, is quinophthalone sulfonic acid. For the reaction between quinaldine and phthalaldehydic acid, see *Nencki*, Ber. **29**, 187.

With oxalic ester and potassium ethylate, quinaldine and lepidine condense to the yellow 2- and 4-**quinolinepyruvic acid esters** (*quinaldineoxalic ester* and *lepidineoxalic ester*), $(C_9H_6N)CH{:}CH(OH)COOH$, m.p. 131° and 195°, which are yellow in alkali but colorless in acid solution, probably due to rearrangement to the keto form (*Wislicenus*, *Kleisinger*, Ber. **42**, 1140).

2-Phenylquinoline, m.p. 84°, b.p. 263°, from aniline and cinnamaldehyde by heating with hydrochloric acid at 200°, is oxidized by $KMnO_4$ to benzoylanthranilic acid. For the decomposition of its methyl iodide addition product to *o*-methylaminodibenzoylmethane, see p. 231.

3-**Phenylquinoline**, m.p. 52° (*Friedländer*, *Gohring*, Ber. **16**, 1836).

4-**Phenylquinoline**, m.p. 61°, derived from its 2-carboxylic acid, is closely related to several decomposition products of the cinchona alkaloids (p. 351) (*Koenigs*, *Nef*, Ber. **20**, 622). **Nitrophenylquinoline**, $NO_2C_6H_4C_9H_6N$, m.p. 159°, from isodiazonitrobenzene and quinoline (*Kühling*, Ber. **29**, 168). **4-Phenylquinaldine**, 4-*phenyl-2-methylquinoline*, m.p. 99°, is produced by the condensation of benzoylacetone with aniline (*Beyer*, Ber. **20**, 1771); its *phthalone*, $C_9H_5N(C_6H_5)CH{:}(C_2O_2C_6H_4)$, is oxidized by chromic acid to **4-phenylquinoline-2-carboxylic acid**, which gives 4-phenylquinoline when decarboxylated. **2-Phenyl-4-methylquinoline**, m.p. 65° (*John*, *Noziczka*, J.pr. **111**, 65), is obtained from flavenol (see below) by distillation with zinc dust. Its *p*-amino derivative, *p*-**flavaniline**, 2-(*p-aminophenyl*)-4-*methylquinoline*, $C_9H_5N(CH_3)(C_6H_4NH_2)$ (*Fischer*, Ber. **19**, 1038), whose yellow monoacid salts have been used as dyes (*Fischer*, *Rudolph*, Ber. **15**, 1500), results from the condensation of *o*-aminoacetophenone with *p*-aminoacetophenone. Nitrous acid converts flavaniline to **flavenol**, 2-(*p-hydroxyphenyl*)-4-*methylquinoline*, $C_9H_5(CH_3)(C_6H_4OH)N$. For *o*-**flavaniline**, see *Camps*, Ber. **32**, 3231.

Various isomeric **biquinolines**, $(C_9H_6N)_2$, have been prepared by digestion of quinoline with sodium, by the action of copper-bronze on iodoquinolines, by passage of quinoline vapor through an incandescent tube, by application of the

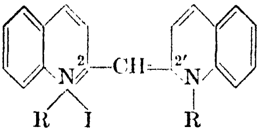
Skraup synthesis to benzidine and other diaminobiphenyls, and by the reaction of quinolineacetaldehyde with *o*-aminobenzaldehyde according to method *2* (p. **227**) (*Weidel*, Ber. **8**, 121; *Zimmermann*, *Müller*, Ber. **17**, 1965; *Koenigs*, *Nef*, Ber. **20**, 634; *v. Niementowski*, *Seifert*, Ber. **38**, 762; *Einhorn*, *Sherman*, Ann. **287**, 38, and others).

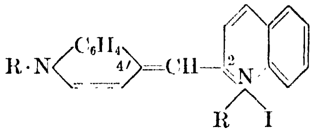
Diquinolylquinoline, $C_9H_6N \cdot C_9H_5N \cdot C_9H_6N$, m.p. 151°, is obtained from 4-acetoacetylquinoline (p. 241) with 2 molar proportions of *o*-aminobenzaldehyde (*Weidel*, Mo. **17**, 401).

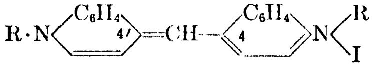
2,2′-Diquinolylmethane, m.p. 102°, from 2-chloroquinoline and quinaldine at 180–200°, together with a little triquinolylmethane (*Scheibe*, Ber. **54**, 786).

Triquinolylmethane, $CH(C_9H_6N)_3$, m.p. 202°, from pararosaniline by the *Skraup* reaction (*Noelting*, *Schwartz*, Ber. **24**, 1606; *Rhoussopoulos*, Ber. **24**, 2267).

The *cyanine*, *isocyanine* and *pseudoisocyanine* dyes* mentioned on p. 231, are derivatives of 2,2′-, 4,4′- or 2,4′-diquinolylmethanes. They are formed by the action of alkali on a mixture of *methylquinolinium iodides* and *alkyl*-2- or 4-*methylquinolinium iodides*. (Summary of the literature: *König*, *Treichel*, J.pr. **102**, 63.) These dyes, called collectively *quinocyanines*, have the following structures (*Scheibe*, Ber. **54**, 786; *König*, Ber. **55**, 3293; *Rosenhauer*, Ber. **59**, 2356):

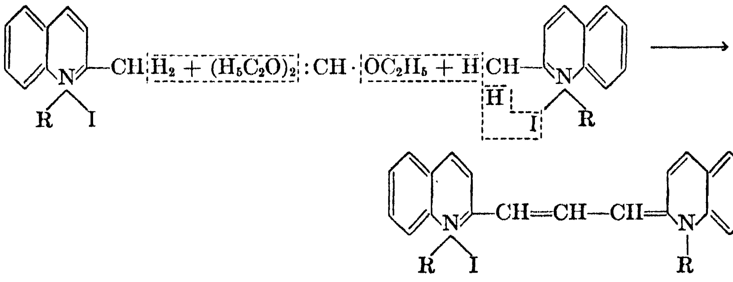






In the formation of these compounds, *methylenedihydroquinolines* (quinolone methides) are known to be intermediate products (*Rosenhauer*, Ber. **59**, 2356). The methine link joining the two heterocyclic rings can be lengthened by one or more vinyl groups. The dyes so obtained are called *pinacyanols* (joined in the 2,2′-position) or *dicyanines* (joined in the 4,4′-position), although the name strepto-mono(di, tri)-vinylenequinocyanines would be a more reasonable one (*König*, Ber. **55**, 3309).

The validity of the above formulas is most clearly demonstrated by the formation of these dyes from 1-alkyl-2-methylquinolinium iodide by the action of orthoformic acid ester in the presence of acetic anhydride or zinc chloride (*König*, Ber. **55**, 3293); technically, formaldehyde, chloroform, bromoform, or iodoform is used (Ger. Pat. 172118, 1905, Frdl. **VIII**, 534; Ger. Pat. 175034, 1906, Frdl. **VIII**, 535; Ger. Pat. 200207, 1907, Frdl. **IX**, 281; *Fischer*, J.pr. **98**, 213):



The immediate conversion of methylenedihydroquinolines to pinacyanols with iodoform or chloroform indicates that they are intermediate products in the above reaction also (*Rosenhauer*, Ber. **59**, 2357).

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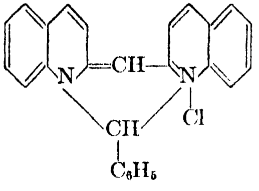
* *H. Bucherer*, Lehrbuch der Farbenchemie (Spamer, Leipzig, 1921; *H. E. Fierz-David;* Künstliche organische Farbstoffe (Springer, Berlin, 1926); *Cain*, *Thorpe*, Synthetic Dyestuffs (Griffin, London, 1933).

The structure of the dyes known as *apocyanines*, which are obtained from alkylquinolinium iodides with alcoholic KOH, is not certain (*Kaufmann, Strübin*, Ber. **44**, 690; *König*, Ber. **55**, 3294).

Quinoline red (I)


(I)

is produced by the condensation of quinaldine, quinoline, and benzotrichloride (*Vongerichten, Hofmann*, Ber. **45**, 3447) and also by the action of benzylidene chloride on 2,2′-diquinoylmethane (*Scheibe*, Ber. **54**, 786).

A large number of these blue and red dyes, especially *ethyl red*, from 1-alkylquinolinium iodide and 1-alkyl-2-methylquinolinium iodide, and the pinacyanols, are technically important as sensitizers for photographic plates. For individual members of these dyestuff groups, see the books on organic dyes cited on the preceding page.

HALOGEN, SULFO, ARSENO AND NITRO DERIVATIVES OF THE QUINOLINES. Halogen, sulfo, and nitro derivatives containing the substituents in the benzene ring are prepared by the methods customarily used for the introduction of such groups into benzene and naphthalene, or by synthesis from the correspondingly substituted benzenes (p. 226). For the nitration of quinoline, see *Kaufmann, Hüssey*, Ber. **41**, 1735. It is more difficult to introduce halogen, nitro and sulfo groups into the pyridine nucleus of quinoline. *Py*-Chloroquinolines are obtained from *Py*-hydroxyquinolines with PCl_5. 3-Halogen derivatives are also formed by heating with sulfur chloride or bromide. As in the pyridine series, 2-chloroquinolines are produced from 1-alkyl-2-quinolones with phosphorus chlorides (*Fischer*, Ber. **32**, 1297; **35**, 3678). The halogen atoms in the 2- and 3-positions are displaced by OH, NHR, and the like with remarkable ease (*cf.* halogenopyridines, p. 206).

2-Chloroquinoline, m.p. 38°, b.p. 267°, from carbostyril, 1-methyl-, or 1-ethylquinolone and PCl_5 (*Friedländer, Ostermaier*, Ber. **15**, 333; *Fischer*, Ber. **31**, 611). **3-Chloroquinoline,** b.p. 255°, from quinoline and sulfur chloride, together with the compound called thioquinanthrene, $(C_9H_5N)_2S_2$, and trichloroquinoline (*Edinger*, Ber. **29**, 2456; *Edinger, Ekeley*, J.pr. **66**, 209). **2-Bromoquinoline,** m.p. 49° (*Claus, Pollitz*, J.pr. **41**, 41). **3-Bromoquinoline,** m.p. 13°, b.p. 276°, by the action of sulfur bromide on quinoline or by heating quinolinium chloride with bromine (*Claus*, J.pr. **45**, 222; *Claus, Howitz*, J.pr. **50**, 232; *Edinger*, Ber. **29**, 2459). **4-Chloroquinoline,** m.p. 34°, from 4-quinolinol with PCl_5 (p. 239), from 4-aminoquinoline by diazotization in hydrochloric acid and from quinoline-N-oxide with sulfuryl chloride (*Meisenheimer*, Ber. **59**, 1852); **4-iodoquinoline,** m.p. 100°, is similarly prepared from 4-aminoquinoline (*Claus, Frobenius*, J.pr. **56**, 193). **4-Bromoquinoline,** m.p. 30°, from 4-quinolinol with PBr_3 (*Claus, Howitz*, J.pr. **50**, 232; *Claus, Frobenius*, J.pr. **56**, 192). **2-Iodo-1-methylquinolinium iodide,** $C_9H_6IN \cdot ICH_3$, m.p. 212°, from 2-chloroquinoline with methyl iodide (*Roser*, Ann. **282**, 376). **6-Chloroquinoline,** m.p. 40°, b.p. 262° (740 mm.) (*v. Braun, Grabowski, Rawicz*, Ber. **46**, 3171). **6-Bromoquinoline,** m.p. 24°, b.p. 284°. **8-Chloro-** and **8-bromoquinoline,** b.p. 288° and 302° (*Claus, Schöller*, J.pr. **48**, 141; *Claus, Günther*, J.pr. **55**, 104). **3-Chloro-2-methylquinoline,** m.p. 72°, from methylindole, chloroform, and sodium alcoholate (*Reissert*, Ber. **21**, 1942). **2,3-Dichloroquinoline,** m.p. 105°, from hydrocarbostyril with PCl_5. **2,3,4-Trichloroquinoline,** $C_9H_4Cl_3N$, m.p. 107°, from malonanilic acid with PCl_5 (p. 229) (*Rügheimer*, Ber. **17**, 737).

QUINOLINESULFONIC ACIDS. The preferred points of entry of the sulfonic acid group are the 8-position, then the 6- and the 5-. The 2- and 4-quinolinesulfonic acids are formed by oxidation of the mercaptans (p. 240) or by the reaction of 2- and 4-halogenoquinolines with alkali sulfites (*Besthorn, Geisselbrecht*, Ber. **53**, 1017). When heated to 300°, quinoline-8-sulfonic acid rearranges to the 6-sulfonic acid.

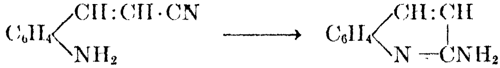
Quinolinesulfonic acids, colorless needles, all melting over 270°.

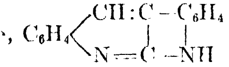
Arsenic acids and **arseno derivatives** of quinoline have been obtained from the corresponding amino compounds (*Binz*, *Räth*, Ann. **453**, 238).

NITROQUINOLINES. The same considerations hold for the introduction of the nitro group into quinoline and its derivatives as for the introduction of the sulfonic acid group. The preparation of 3-nitroquinoline from *o*-aminobenzaldehyde and *as*-isonitrosonitroethane is an interesting variation of the *Friedländer* quinoline synthesis (Ger. Pat. 335197, 1919, Frdl. **XIII**, 818).

3-**Nitroquinoline**, m.p. 128°. 5-, 6-, 7-, 8-**Nitroquinoline**, m.p. 72°, 148°, 133°, and 89°. The latter is obtained by nitration of quinoline. Energetic nitration gives dinitroquinolines.

AMINOQUINOLINES. *Bz*-Aminoquinolines are prepared by reduction of the corresponding nitroquinolines. The 2- and 4-amino derivatives are obtained by heating 2- and 4-chloro- or bromoquinolines with ammonia or amines. The method used in the pyridine series for the direct introduction of the amino group, heating with sodium amide in xylene solution, can also be applied in the quinoline series (Ger. Pat. 374291, 1914, Frdl. **XIV**, 527; *Tschitschibabin*, *Witkowsky*, *Lapschin*, Ber. **58**, 803). 2-Aminoquinolines are also formed by synthesis from *o*-aminocinnamic acid nitriles (*Pschorr*, *Wolfes*, Ber. **32**, 3399):



Cf. the formation of quinindoline, , by reduction of *o*,*o*′-dinitro-*α*-cyanobibenzyl, $NO_2C_6H_4CH_2CH(CN)C_6H_4NO_2$ (p. 267).

The 2- and 4-aminoquinolines often react in the tautomeric form as iminodihydroquinolines. The statements made on p. 197 concerning the tautomerism of pyridine, especially in relation to 2- and 4-aminopyridine, hold also for the quinoline series. (*Cf. Diepolder*, *Deuerlein*, J.pr. **106**, 61; and *Tschitschibabin*, Ber. **54**, 822).

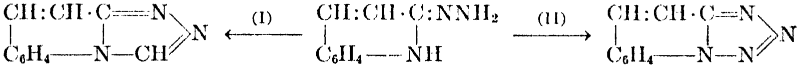
2-**Aminoquinoline**, m.p. 129.5°, from quinoline with sodium amide [*Tschitschibabin*, *Sazepina*, J.Russ.Phys.Chem.Soc. **50** (1918), 553], from cinnamic acid nitrile with sodium ethylate (see above), from 2-chloroquinoline by heating with ammonia and ammonium carbonate at 200° (together with carbostyril) and from 2-phenylhydrazinoquinoline or hydrazoquinoline (see below) by reductive decomposition (*Claus*, *Schaller*, J.pr. **56**, 204; *Pschorr*, Ber. **31**, 1297), is hydrolyzed by concentrated alkali to NH_3 and carbostyril. When treated with nitrating acids, 2-aminoquinoline yields 2-**quinolylnitramide**, m.p. 225° (dec.); this rearranges at higher temperatures under the influence of concentrated sulfuric acid to 6-**nitro-2-aminoquinoline**, m.p. 261° (*Tschitschibabin*, *Witkowsky*, *Lapschin*, Ber. **58**, 803). 2-**Anilinoquinoline**, $(C_9H_6N)\cdot NHC_6H_5$, m.p. 98°, from 2-chloroquinoline and aniline at 200°.

2-**Amino-3-phenylquinoline**, m.p. 156° (corr.), is obtained from *α*-phenyl-*o*-nitrocinnamic acid nitrile by reduction, and by condensation of *o*-acetamidobenzaldehyde with benzyl cyanide.

3-**Aminoquinoline**, dimorphous, m.p. 84° and 94°, from 3-quinolinecarboxylic acid amide with NaOBr (*Mills*, *Watson*, J. **97**, 741). 3-**Aminoquinaldine**, m.p. 160°, from the oxime of 3-acetylquinaldine by a *Beckmann* rearrangement (*Stark*, Ber. **40**, 3425). 3-Aminoquinolines have also been prepared from aromatic *o*-amino aldehydes and N-*acetonyl*- or N-*phenacylphthalimide* by the *Friedländer* method (*Berlingozzi*, Gazz. **53**, 369).

4-**Aminoquinoline** (1 H_2O), m.p. 70° (anhydrous, 154°), is formed from cinchoninic acid amide with bromide and alkali (*Claus*, *Frobenius*, J.pr. **56**, 181). 4-**Aminoquinaldine**, m.p. 270° (*Conrad*, *Limpach*, Ber. 21, 1980). 4-**Amino-2-phenylquinoline**, m.p. 168°, from the corresponding carboxylic acid azide by the *Curtius* reaction (*John*, Ber. **59**, 1447). 5-, 6-, and 8-**Aminoquinoline**, m.p. 110°, b.p. 184° (10 mm.); m.p. 118°, b.p. 187° (11 mm.); m.p. 65°, b.p. 160° (20 mm.) (*Kaufmann*, *Zeller*, Ber. **50**, 1627). 6-**Methoxy-4-aminoquinoline**, $C_9H_5N(OCH_3)(NH_2)$, m.p. 120°, from quininic acid amide with KOBr (*Hirsch*, Mo. **17**, 327).

HYDRAZINOQUINOLINES are obtained from 2- and 4-chloroquinoline by heating with hydrazine or phenylhydrazines (*Ephraim*, Ber. **24**, 2817; *Marckwald, Meyer*, Ber. **33**, 1885). **2-Hydrazinoquinoline**, $(C_9H_6N)\cdot NH\cdot NH_2$, m.p. 135°, behaves in some reactions as a hydrazidine; with formic acid it gives *s*-triazolo[4,3-*a*]quinoline, naphtriazole (I), m.p. 175°, and with nitrous acid, tetrazolo[*a*]quinoline, naphtetrazole (II), m.p. 157° (*cf.* p. 214):



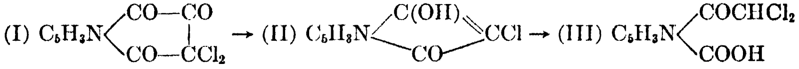
The tetrazoloquinoline is converted quantitatively into *tetrazole* by oxidation with $KMnO_4$ (*Marckwald, Meyer*, Ber. **33**, 1890).

2-Hydrazinolepidine, $[C_9H_5(4\text{-}CH_3)N][2]NHNH_2$, m.p. 146°. **4-Hydrazinoquinaldine**, m.p. 118°. **2,2′-Hydrazoquinoline**, $(C_9H_6N)NH\cdot NH(C_9H_6N)$, m.p. 229°, and **2,2′-hydrazolepidine**, m.p. 265°, are formed together with the hydrazines when the 2-chloroquinolines are heated with hydrazine hydrate; on oxidation they yield **2-azoquinoline** and **2-azolepidine**, m.p. 230° and 235°, and on reduction with zinc dust and hydrochloric acid they give 2-aminoquinoline and 2-aminolepidine. **2-Phenylhydrazinoquinoline**, $(C_9H_6N)NHNHC_6H_5$, m.p. 191°, oxidizes to **phenylazoquinoline**, m.p. 93° (*Ephraim*, Ber. **24**, 2817).

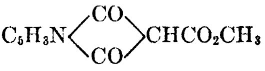
HYDROXYQUINOLINES, QUINOLINOLS. The hydroxyquinolines have the properties of both bases and phenols.

Quinolines hydroxylated in the benzene nucleus, which are also called quinophenols or hydroxybenzoquinolines, are prepared by the *Döbner-Miller* synthesis from aminophenols, by rearrangement of *Bz*-nitroquinolines, and by fusion of quinolinesulfonic acids with KOH. Into the quinolinols so obtained further hydroxyl groups can be introduced by fusion with KOH (*Edinger, Bühler*, Ber. **42**, 4316). **8-Quinolinol**, $C_6H_3(OH):(C_3H_3N)$, m.p. 75°, b.p. 266°, from 8-quinolinesulfonic acid (*Fischer*, Ber. **16**, 712). **6-Quinolinol**, m.p. 194°, from xanthoquinic acid (p. 243) by decarboxylation; its alkyl iodide addition product yields stable quinolinium hydroxides (*cf.* p. 230), although the 4-alkoxyquinolines behave in this respect like the other quinoline derivatives (*Howitz, Bärlocher*, Ber. **36**, 456; *Decker, Engler*, Ber. **36**, 1169). **Loretin**, a substitute for iodoform, is **7-iodo-8-hydroxyquinoline-5-sulfonic acid**, $C_6H(OH)I(SO_3H):(C_3H_3N)$ (*Claus, Bowmann*, J.pr. **55**, 457).

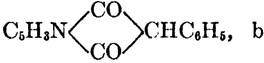
Like the naphthols, the *Bz*-quinolinols are converted to chlorinated quinones by treatment with chlorine in glacial acetic acid according to the *Zincke* method; these behave similarly to the naphthalene derivatives, which form indenes, in their transformation to **pyrindene** derivatives, compounds containing condensed pyridine and indene rings. Thus, by a series of steps, 6-quinolinol and chlorine yield **dichloroquinolinetrione** (I). When boiled with water this gives **3-chloro-2-hydroxypyrindone** (II), from which by ring-fission **(dichloroacetyl)picolinic acid** (III) is obtained (*Zincke*, Ann. **290**, 321):

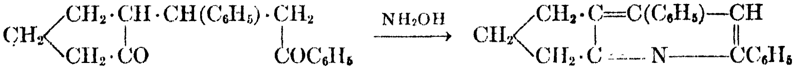


Pyrindene derivatives have also been synthesized from benzene derivatives. **5,7-Dioxo-6,7-dihydro-1,5-pyrindene-6-carboxylic acid ester,**



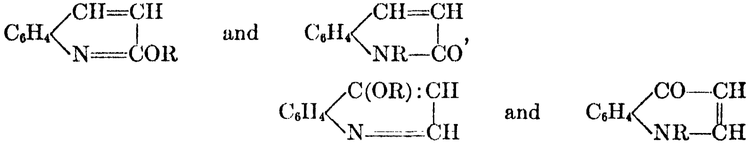
$$C_5H_3N\left<\begin{matrix}CO\\CO\end{matrix}\right>CHCO_2CH_3$$

from quinolinic acid ester with acetic ester and sodium (*Bittner*, Ber. **35**, 1411). **6-Phenyl-2,5-pyrindene-5,7-dione**,  $C_5H_3N\left<\begin{matrix}CO\\CO\end{matrix}\right>CHC_6H_5$, by rearrangement of benzylidenecinchomeronide, $\overline{OCO\cdot C_5H_3N\cdot C}:CHC_6H_5$, the condensation product of cinchomeronic acid anhydride with phenylacetic acid (*Fels*, Ber. **37**, 2137). **2,4-Diphenyl-6,7-dihydro-1,5-pyrindene**, from the diketone, which is formed by addition of cyclopentanone to benzylideneacetophenone (chalcone), by treatment with hydroxylamine (*Stobbe, Volland*, Ber. **35**, 3973):



$$CH_2\left<\begin{array}{l}CH_2\cdot CH\cdot CH(C_6H_5)\cdot CH_2\\ CH_2\cdot CO \qquad\qquad\quad COC_6H_5\end{array}\right. \xrightarrow{NH_2OH} CH_2\left<\begin{array}{l}CH_2\cdot C{=}C(C_6H_5){-}CH\\ CH_2\cdot C{-}N{-}CC_6H_5\end{array}\right.$$

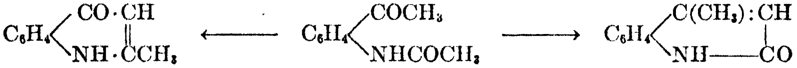
The quinolines hydroxylated in the pyridine nucleus are weaker bases and phenolic acids than the *Bz*-quinolinols. As in the case of the pyridols (or pyridones, p. 209), it is uncertain whether the 2- and 4-quinolinols have the hydroxy or oxo form. Ethers of the two forms—*e.g.*, carbostyril and pseudocarbostyril—can be obtained, and can be rearranged to one another (see below, and *Tschitschibabin, Jeletzky*, Ber. **57**, 1158):



$$C_6H_4\left<\begin{array}{l}CH{=}CH\\ N{=}COR\end{array}\right. \text{ and } C_6H_4\left<\begin{array}{l}CH{=}CH\\ NR{-}CO\end{array}\right.,$$

$$C_6H_4\left<\begin{array}{l}C(OR){:}CH\\ N{=}CH\end{array}\right. \text{ and } C_6H_4\left<\begin{array}{l}CO{-}CH\\ NR{-}CH\end{array}\right.$$

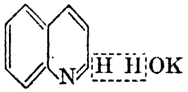
Besides the ring-synthetic methods (p. 226), 2- and 4-quinolinols are obtained, according to *Camps* (Z.physiol.Chem. **33**, 400; Ber. **32**, 3228), by digesting N-acetyl-*o*-aminoacetophenone with lye. N-Acetyl-*o*-aminoacetophenone gives both 2- and 4-hydroxy derivatives:



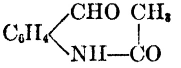
$$C_6H_4\left<\begin{array}{l}CO\cdot CH\\ NH\cdot CCH_3\end{array}\right. \longleftarrow C_6H_4\left<\begin{array}{l}COCH_3\\ NHCOCH_3\end{array}\right. \longrightarrow C_6H_4\left<\begin{array}{l}C(CH_3){:}CH\\ NH{-}CO\end{array}\right.$$

With appropriate starting materials, this synthesis can also be used for the preparation of hydroxyquinolinecarboxylic acids (see below).

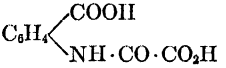
Hydroxyl groups are easily introduced into quinoline and its homologues by heating them with barium or potassium hydroxide to the boiling point (*Tschitschibabin*, Ber. **56**, 1879; Ger. Pat. 406208, 1922, Frdl. **XIV**, 515):



2-Quinolinol, carbostyril, m.p. 199°, the lactime or lactam of *o*-aminocinnamic acid, is prepared by reduction of *o*-nitrocinnamic acid (*Friedländer, Ostermaier*, Ber. **14**, 1916). It is also obtained from *o*-acetamidobenzaldehyde (I) with aqueous sodium hydroxide,

(I) 

$$C_6H_4\left<\begin{array}{l}CHO\ CH_3\\ NH{-}CO\end{array}\right.$$

 (II)

$$C_6H_4\left<\begin{array}{l}COOH\\ NH\cdot CO\cdot CO_2H\end{array}\right.$$

from 2-chloroquinoline by heating with water, and from quinoline by warming with calcium oxychloride solution (*Roos*, Ber. **21**, 619) or by boiling with barium or potassium hydroxide (*Tschitschibabin*, Ber. **56**, 1879). Its salts with alkalis and acids are decomposed by water. Potassium permanganate oxidizes it to N-oxalylanthranilic acid (II), and Na and alcohol reduce it to tetrahydroquinoline.

Carbostyril methyl ether, b.p. 247°, *ethyl ether*, b.p. 256°, are oils, produced by the action of alkyl iodides on the Na or Ag salt of carbostyril, from 2-chloroquinoline with sodium alcoholates, and also from *o*-aminocinnamic acid esters with alcoholic zinc chloride. N-*Methyl*-2(1)-*quinolone, pseudocarbostyril methyl ether*, m.p. 71°, *ethyl ether*, m.p. 54°, are formed from alkyl iodides with free carbostyril, and also from methyl- and ethylquinolinium iodide with sodium hydroxide solution and potassium ferricyanide (*cf.* p. 230). N-Methylquinolone is also prepared by heating ethoxyquinoline with methyl iodide (*Knorr*, Ber. **30**, 930). With P_2S_5 it gives N-*methylthioquinolone*, $C_9H_6SN(CH_3)$, m.p. 118° (*Gutbier*, Ber. **33**, 3358).

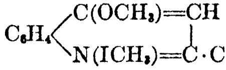
8-**Nitrocarbostyril**, m.p. 168°, is obtained from nitrocoumarin with alcoholic NH_3; for isomeric nitrocarbostyrils, see *Decker*, J.pr. **64**, 85; *Decker, Stavrolopoulos*, J.pr. **68**, 100. 2,6-**Quinolinediol**, 6-*hydroxycarbostyril*, m.p. over 300°, by condensation of *o*-amino-*m*-hydroxycinnamic acid, which results from the electrolytic reduction of *o*-nitrocinnamic acid.

3-**Quinolinol**, (*Bargellini, Settimj*, Gazz. **53**, 601), m.p. 198°, from diazotized 3-aminoquinoline (*Mills, Watson*, J. **97**, 741). 2-**Methyl**-3-**quinolinol**, 3-*hydroxyquinaldine*, has been prepared by the condensation of *o*-aminobenzaldehyde and chloroacetone in aqueous sodium hydroxide (*Koenigs, Stockhausen*, Ber. **35**, 2554).

4-**Methylcarbostyril**, 4-**methyl**-2-**hydroxyquinoline**, or 2-**lepidone**, $C_9H_6(CH_3)ON$, m.p. 223°, b.p. 270° (17 mm.), from 4-methylquinoline by heating with caustic alkali (*Tschitschibabin*, Ber. **56**, 1879; Ger. Pat. 406208, 1922, Frdl. **XIV**, 515) or from the anilide of acetoacetic ester (p. 228); its lactime ether, 2-methoxy-4-methylquinoline, b.p. 276°, from 2-chlorolepidine with $NaOCH_3$; its lactam ether, N-methyl-2(1)-lepidone, m.p. 131°, from acetoacetic ester and methylaniline (p. 229) or from ethoxylepidine by heating with methyl iodide (*Knorr*, Ber. **30**, 931). 7-**Amino**-2(1)-**lepidone**, m.p. 270°, from *m*-phenylenediamine and acetoacetic ester (*Besthorn, Byvanck*, Ber. **31**, 798). 2,2′-**Dihydroxy**-4,4′-**dimethylbiquinoline** or **bilepidone**, $[C_9H_5(CH_3)ON]_2$, from benzidine and acetoacetic ester (*Heidrich*, Mo. **19**, 690).

4-**Quinolinol**, **kynurine**, $C_9H_7ON(+\ 3H_2O)$, m.p. 201°, is prepared by heating kynurenic acid (p. 242) and by oxidation of cinchonine or cinchoninic acid (*Skraup*, Mo. **10**, 726). It is also synthesized from N-formyl-*o*-aminoacetophenone by the methods given on p. 227 (*Camps*, Z.physiol.Chem. **33**, 402). With PCl_5 it gives 4-chloroquinoline (p. 235), from which 4-methoxyquinoline, m.p. 31°, b.p. 245°, is obtained with sodium methylate. The latter, which is also formed from 4-quinolinol with diazomethane, rearranges when heated to 300–310° to N-methyl-4(1)-quinolone, m.p. 143° (*Meyer*, Mo. **27**, 255).

2-**Methyl**-4-**quinolinol**, 4-**hydroxyquinaldine**, 4(1)-**quinaldone**, $C_9H_6(CH_3)ON$ $(+2\,H_2O)$, m.p. 231°, from acetoacetic ester anil (p. 229), also forms two isomeric ethers: 4-methoxyquinaldine, b.p. 298°, and N-methylquinaldone, m.p. 175° (*Conrad, Eckhardt*, Ber. **22**, 78). With methyl iodide both ethers give the same quinolinium salt:



$$C_6H_4\begin{array}{l}\diagup C(OCH_3){=}CH\\ \qquad\qquad\qquad\quad\;|\\ \diagdown N(ICH_3){=}C\cdot CH_3\end{array}$$

which yields N-methylquinaldone when treated with alkali (*Knorr*, Ber. **30**, 922); *cf.* the similar behavior of the antipyrines, pyridones, *etc.*, pp. 106, 209).

Both isomers, quinaldone and lepidone, are produced from *o*-acetamidoacetophenone with aqueous sodium hydroxide according to the reaction formulated on p. 227.

6-**Quinolinol**, m.p. 195° [*Scheunemann*, Arch.exptl.Path.Pharm. **100** (1924), 51]. 8-**Quinolinol**, m.p. 95° (Brit. Pat. 198462, 1922). The ability of 8-quinolinol to form very sparingly soluble complex salts with most metal salts is used for its detection and separation [*Berg*, J.pr. **115**, 178; Z.anal.Chem. **70** (1927), 341).

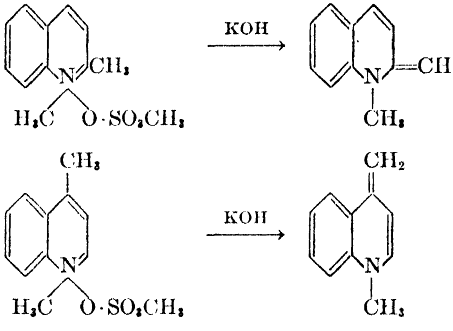
Two alkaloids of the angostura bark, *galipine* and *cusparine* (p. 350), are derivatives of 4-quinolinol (*Späth*, Z.angew.Chem. **1928**, 1259; Mo. **42**, 89).

4,6-**Quinolinediol**, is prepared by saponification of 6-methoxy-4-quinolinol, which is obtained from 6-methoxy-4-aminoquinoline with nitrous acid (*Hirsch*, Mo. **17**, 327).

2,3-**Quinolinediol**, m.p. 258°, from N-oxalyl-*o*-toluidine by fusion with sodium alcoholate (*Madelung*, Ber. **45**, 3524) or by enlarging the indole ring in isatin by the action of diazomethane in ethereal solution (*Heller*, Ber. **59**, 704).

2,4-**Quinolinediol**, 4-*hydroxycarbostyril*, sublimable, is formed from 4-bromocarbostyril with KOH, from *o*-aminophenylpropiolic acid by warming with sulfuric acid from anthranilic acid ester by condensation with acetic ester or malonic ester and sodium (*Erdmann*, Ber. **32**, 3570) and from *o*-acetylanthranilic acid ester with sodium [*Camps*, Arch.Pharm. **237** (1900), 659; Ger. Pat. 117167, 1900). It also results from carbostyril by energetic treatment with caustic potash (Ger. Pat. 406208, 1922). It couples with diazo compounds to give azo dyes (Ger. Pat. 165327, 1904).

METHYLENEDIHYDROQUINOLINES or **quinolone methides** are very reactive. They correspond to the methylenedihydropyridines or pyridone methides and are prepared similarly from 1-alkyl-2- and 4-methylquinolinium iodides or sulfates by the action of alkali. The simplest members of this group are shown in the following equations (*Rosenhauer*, Ber. **59**, 946):



These very reactive methylene compounds occur as intermediate products in the formation of cyanine and pinacyanole dyes (p. 234).

1-Methyl-2-methylene-1,2-dihydroquinoline, 1-methyl-2-quinolone methide, bright yellow, m.p. 72°. Analogous bases from 1,2,4-trimethyl- and 1,2,4,6-tetramethylquinolinium iodide, bright yellow, m.p. 60° and 45°. Reduction of its 3-nitroso derivative gives **2,3,4-quinolinetriol,** which is oxidized by ferric chloride to **quinisatinic acid** and **quinisatin** or **quinolinetrione** (*Baeyer, Homolka*, Ber. **17**, 985).

AMINOQUINOLINOLS. 2-Amino-4-quinolinol, m.p. 304° (not sharp), by isomerization of *α*-cyano-*o*-aminoacetophenone (*Gabriel*, Ber. **51**, 1500).

Plasmochin is 8-(*α*-methyl-*δ*-diethylaminobutyl)-6-methoxyquinoline (*Zernik*, Pharm.Zentralhalle **68**, 70). It has a specific action against malaria parasites, especially against the sexual forms, the gametes, which are only slightly affected by quinine. It is usually used in combination with quinine as *plasmochin compositum* (*Hörlein*, Naturwiss. **14** (1926), 1154; *Mühlens, ibid.*, 1162].

Mercaptoquinolines are usually obtained from the reaction of the corresponding chloroquinolines with thiourea (*Rosenhauer, Hoffmann, Heuser*, Ber. **62**, 2730).

2-Quinolinethiol, yellow, m.p. 175°, and **6-methyl-2-quinolinethiol,** m.p. 210°, from 2-chloroquinoline and 2-chlorotoluquinoline with KSH (*Fischer*, Ber. **32**, 1305) or thiourea (*Rosenhauer, Hoffmann, Heuser*, Ber. **62**, 2730).

2-Phenyl-4-quinolinethiol, m.p. 176°, from the corresponding chloroquinoline (*John*, J.pr. **119**, 49).

QUINOLINECARBOXALDEHYDES AND QUINOLINE KETONES. 8-Quinolinecarboxaldehyde, $CHO \cdot C_6H_3(C_3H_3N)$, m.p. 95°, see *Howitz, Schwenk*, Ber. **38**, 1280. **2-Quinolinecarboxaldehyde,** m.p. 71°, is obtained from 2-quinolineacrylic acid (p. 233) with $KMnO_4$; its oxime, m.p. 189°, from *o*-aminobenzaldehyde with isonitrosoacetone according to method *2* (p. 226; *Pfitzinger* J.pr. **66**, 264). For the preparation of diphenyl-2-quinolylmethane dyes, see *Dey, Dutt*, J.IndianChem.Soc. **5** (1929), 535.

Py-**Quinoline ketones** are prepared according to method *2*, p. 226, from *o*-aminobenzaldehyde with *β*-diketones. 4-Quinoline ketones have also been obtained from cinchoninic acid esters with Grignard reagents or from the condensation product of acetoacetic ester with acetic ester by ketone fission (*Rabe, Pasternack, Kindler*, Ber. **50**, 144). **3-Acetylquinaldine,** $C_9H_5N(CH_3)(COCH_3)$, m.p. 57.5° (*Eliasberg, Friedländer*, Ber. **25**, 1756). **3-Benzoylquinaldine,** $C_9H_5(CH_3)(COC_6H_5)$, m.p. 62° (*Stark*, Ber. **42**, 715). **3-Acetylcarbostyril,** $C_9H_6N(COCH_3)O$, **m.p. 232°,** from *o*-aminobenzaldehyde and acetoacetic ester (*Fried-*

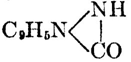
länder, Gohring, Ber. **16,** 1838). **2-Benzoylquinoline,** $(C_9H_6N)COC_6H_5$, m.p. 111°, from quinaldic acid chloride with C_6H_6 and $AlCl_3$ (*Besthorn,* Ber. **41,** 2001). **4-Acetoacetylquinoline,** $C_9H_6N(COCH_2COCH_3)$, m.p. 65°, b.p. 206° (17 mm.), from cinchoninic acid ester (see below), acetone and sodium ethylate, condenses with phenylhydrazine to *phenylquinolylmethylpyrazole,* m.p. 120°, and with 2 mols of *o*-aminobenzaldehyde to *diquinolylquinoline* (p. 234). **4-Quinoline pyrryl ketone** (*Karrer,* Ber. **50,** 1499).

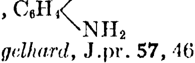
QUINOLINECARBOXYLIC ACIDS. The quinolinecarboxylic acids behave like aminocarboxylic acids. Those substituted in the benzene ring are synthesized from the aminobenzoic acids (*Niementowski, Orzechowski,* Ber. **28,** 2809); they are also prepared by oxidation of *Bz*-alkylquinolines with chromic acid or by hydrolysis of their nitriles, which are readily obtained by distillation of the corresponding sulfonic acids with KCN. The *Py*-quinolinecarboxylic acids are formed by oxidation of *Py*-alkylquinolines with chromic acid mixture; alkyl groups in the 4-position are oxidizd most readily, those in the 3-position less readily, and those in the 2-position with the most difficulty (*v. Miller,* Ber. **23,** 2254) (p. **230**). Methyl groups in the 2-position can be rendered easier to oxidize by preliminary condensation with formaldehyde (p. **232**). Numerous *Py*-quinolinecarboxylic acids have been obtained by ring-synthesis according to the *Skraup* or *Döbner-Miller* methods (see p. **227**). When heated, the carboxylic acids lose CO_2, and yield the corresponding quinolines. Those containing a carboxyl group in the 2-position are colored red-yellow by ferric sulfate.

8-**Quinolinecarboxylic acid** (for the numbering, see the formula, p. 226), m.p. 187°; 7-**acid,** m.p. 248°; 6-**acid,** m.p. 291°; and 5-**acid,** m.p. 360° (*Lellmann, Alt,* Ann. **237,** 325; *Skraup, Brunner,* Mo. **7,** 139; *Tortelli,* Atti accad. Lincei **1886,** 523; *v. Jakubowski,* Ber. **43,** 3026).

QUINALDIC ACID, 2-quinolinecarboxylic acid (+ $2H_2O$), m.p. 156° (dec.), methyl ester m.p. 86°, from quinaldine or, more advantageously, from the condensation product of quinaldine with formaldehyde (p. **232**) (*Besthorn, Ibele,* Ber. **39,** 2329), is converted by heating with acetic or benzoic anhydride, with loss of CO_2, into a red dye, very sensitive to light (*Besthorn, Ibele,* Ber. **38,** 2127). Quinaldic acid chloride, m.p. 97° (*Besthorn, Ibele,* Ber. **39,** 2330).

3-Quinolinecarboxylic acid, m.p. 273°, is obtained from acridinic acid (see below) (*Doebner, v. Miller,* Ber. **18,** 1640).

CINCHONINIC ACID, 4-quinolinecarboxylic acid, crystallizing with 1 or 2 mols H_2O, m.p. 254°, was first obtained by oxidation of cinchonine with $KMnO_4$ or HNO_3; it has been synthesized by condensation of isatinic acid, acetaldoxime, and aqueous sodium hydroxide (*Pfitzinger,* J.pr. **66,** 263). Chloride, m.p. 68° (*Späth, Spitzer,* Ber. **59,** 1477); anhydride, m.p. 245°; amide, m.p. 177° (*Meyer,* Rec. **44,** 323). Its nitrile, m.p. 95°, is prepared from N-methyldihydrocinchoninic acid nitrile, the reaction product of methylquinolinium iodide with KCN (p. 231), by oxidation with alcoholic iodine solution and decomposition of the resulting methyl iodide addition product of cinchoninic acid nitrile by heat (*Kaufmann, Widmer,* Ber. **44,** 2058; *Kaufmann,* Ber. **51,** 119). The acid is readily converted to quinoline. It is oxidized by $KMnO_4$ to 2,3,4-pyridinetricarboxylic acid. With nitric acid-sulfuric acid it is nitrated to **5-nitrocinchoninic acid,** which is reduced with ammonium sulfide to **5-aminocinchoninic acid.** This acid readily yields an anhydride (analogous to *peri*-naphthostyril, Vol. III, p. 635), m.p. 255° (*Koenigs, Lossow,* Ber. **32,** 717):  $C_9H_5N\left\langle\begin{matrix}NH\\ |\\ CO\end{matrix}\right.$.

Alkylcinchoninic acids result from the condensation of aldehydes with pyruvic acid and anilines (*Döbner,* Ann. **249,** 98; *Döbner, Fettback,* Ann. **281,** 1; *Borsche,* Ber. **42,** 4072) (p. **228**), and also from isatic acid,  $C_6H_4\left\langle\begin{matrix}COCOOH\\ NH_2\end{matrix}\right.$, according to method *2* (p. 226) (*Pfitzinger,* J.pr. **56,** 283; *Engelhard,* J.pr. **57,** 467; *Pfitzinger,* J.pr. **66,** 263). Benzocinchoninic acids are similarly formed from pyruvic acid, aldehydes, and 2-naphthylamine in ether solution. Because of the rapidity of the reaction it may be used for the interception of pyruvic acid as an intermediate product in the fermentation of sugar [*Cagan,* Z.angew.Chem. **39** (1926), 951].

2-Methylcinchoninic acid, *aniluvitoninic acid* (+ H_2O), m.p. 242°, is also obtained from pyruvic acid and aniline (*Beyer,* Ber. **20,** 1769) (*cf.* p. 228) and from isatinic acid with acetone. **2-Phenylcinchoninic acid,** m.p. 209°, from aniline, benzaldehyde, and pyruvic acid or isatinic acid and acetophenone, is used under the name **cinchophen** (atophan) as an antineuralgic agent and gout remedy. According to *J. v. Braun* (*v. Braun, Brauns*, Ber. **60**, 1253), the pharmacological action is related to the 3- or 4-position of the carboxyl group. *Cf.* the investigations on *tetrophan* (*v. Braun*, Ann. **451**, 1). Chloride, m.p. 81–82° [*Rojahn, Schulten*, Arch.Pharm. **264** (1926), 348]. Heating with soda lime gives 2-phenylquinoline (*John*, Ber. **59**, 2709). For hydrogenation products of cinchophen, see *Skita, Wulff*, Ber. **59**, 2683. **Novatophan**, ethyl ester of cinchophen. **Arcanol**, cinchophen + aspirin. 3-**Methyl-** and 3-**phenylcinchoninic acid**, m.p. 254° and 273°, from isatinic acid with propionaldoxime and phenylacetaldoxime, respectively (*Hübner*, Ber. **39**, 982; *Ornstein*, Ber. **40**, 1088). **2,3-Diphenyl-** and **2,3-dimethylcinchoninic acid**, m.p. 295° and 316° (dec.) (*Pfitzinger*, J.pr. **56**, 283).

Quinaldine-3-carboxylic acid, *2-methylquinoline-3-carboxylic acid*, m.p. 234° (dec.), is prepared from *o*-aminobenzaldehyde and acetoacetic ester (*cf.* p. 226) (*Claus, Momberger*, J.pr. **56**, 373).

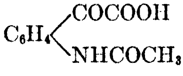
Lepidine-2-carboxylic acid, *4-methylquinoline-2-carboxylic acid*, m.p. 153–154°, from 4-methyl-2-quinolineëthanol (p. 232) by oxidation and loss of CO_2 (*Koenigs, Mengel*, Ber. **37**, 1322).

ACRIDINIC ACID, **2,3-quinolinedicarboxylic acid**, crystallizing with 1 or 2 H_2O, dec. 120–130°, is the product of the oxidation of acridine with $KMnO_4$, as 2,3-pyridinedicarboxylic acid is the product from quinoline. *Diethyl ester*, m.p. 55°, from *o*-aminobenzaldehyde and oxaloacetic ester (*Koller, Strang*, Mo. **50**, 48; *Hozer, v. Niementowski*, J.pr. **116**, 43). Anhydride, m.p. 223°.

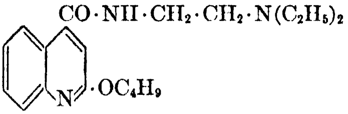
2,4-Quinolinedicarboxylic acid, m.p. 246° (dec.), is prepared from 2-styrylcinchoninic acid (*Doebner, Peters*, Ber. **22**, 3009) by oxidation with $KMnO_4$ and from isatic acid with pyruvic acid (*Pfitzinger*, J.pr. **56**, 308).

3,4-Quinaldinedicarboxylic acid, $C_9H_4(CH_3)N(COOH)_2$, from isatic acid and acetoacetic ester; **2-phenyl-3,4-quinolinedicarboxylic acid**, $C_9H_4(C_6H_5)N(COOH)_2$, from isatic acid with benzoylacetic ester; 3-**carboxymethylquinaldine-4-carboxylic acid**, $C_9H_4(CH_3)N(CH_2COOH)(COOH)$, from isatic acid with levulinic acid, *etc.* (*Engelhard*, J.pr. **57**, 467).

HYDROXYQUINOLINECARBOXYLIC ACIDS. 2-Hydroxyquinoline-3-carboxylic acid, m.p. over 320° (dec.), from *o*-aminobenzaldehyde and malonic acid (p. 226). **2-Hydroxycinchoninic acid**, m.p. 343° (*Aeschlimann*, J. **1926**, 2902), is obtained by fusion of cinchoninic acid with KOH (*cf.* hydroxyquinolinic acid, p. 217), by inner condensation of N-acetylisatic acid (I) and from isatin and malonic acid under various reaction conditions (*Aeschlimann*, J. **1926**, 2902). The silver salts of both acids decompose, when heated, into CO_2 and carbostyril. The local anesthetic **percaine** is a derivative of 2-hydroxyquinoline-4-carboxylic acid (II) (*Mayer*, Chem.Z. **1930**, Fortschrittsber. p. 4).

(I) 

$$C_6H_4\begin{cases}COCOOH\\NHCOCH_3\end{cases}$$

 (II)

Kynurenic acid, **4-hydroxyquinoline-2-carboxylic acid** (+ H_2O), m.p. 289° (*Homer*, J.Biol.Chem. **17**, 509; *Besthorn*, Ber. **54**, 1330; *Späth*, Mo. **42**, 89). occurs in the urine of dogs after the ingestion of meat. It is also formed by the rearrangement of the primary disintegration product of albumen, tryptophan (p. 67) (reaction mechanism: *Ellinger, Matsuoka*, Z.physiol.Chem. **109**, 259; *Matsuoka, Takemura, Yoshimatsu, ibid.*, **143**, 199). It has been synthesized from N-oxalyl-*o*-aminoacetophenone by boiling with aqueous sodium hydroxide (*Camps*, Z. physiol. Chem. **33**, 404). *Methyl ester*, m.p. 224°. It is converted by catalytic hydrogenation over 4-chloroquinoline-2-carboxylic acid to 2-quinolinecarboxylic acid. When fused with alkali it decomposes to CO_2 and kynurine, 4-quinolinol (p. 239); on oxidation it yields kynuric acid or oxalylanthranilic acid. For the synthesis of several methyl homologues of kynurenic acid, see *Robson*, Biochem. J. 22, (1928), 1157. It is remarkable that 8-methylkynurenic acid is metabolized in the body [*Robson*, Biochem.J. 22 (1928), 1165]. **4-Hydroxyquinoline-3-carboxylic acid** is prepared from *o*-formamidophenylpropiolic acid ester by boiling with aqueous sodium hydroxide.

Xanthoquinic acid, 6-hydroxyquinoline-4-carboxylic acid (+ H_2O), m.p. 320° (dec.), is obtained from 6-sulfocinchoninic acid by fusion with alkali. Its 6-methyl ether is called quininic acid, $C_9H_5(OCH_3)(COOH)N$, m.p. 280°, and is formed from quinine and quinidine by oxidation with chromic acid mixture. It has been synthesized by the *Döbner-Miller* reaction from *p*-anisidine, pyruvic acid, and formaldehyde (*Pictet, Misner*, Ber. **45**, 1800).

4-Hydroxyquinoline-3-carboxylic acid, $C_9H_5(CH_3)ON(COOH)$, m.p. 245° (dec.), is produced by the condensation of anthranilic acid with acetoacetic ester (*v. Niementowski*, Ber. **27**, 1396).

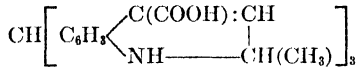
2-Hydroxyquinoline-4-acetic acid, $(C_9H_6ON)CH_2COOH$, m.p. 206° (dec.), is obtained by the condensation of β-ketoglutaric acid dianilide by means of sulfuric acid. *Bz*-Amino-2-hydroxyquinoline-4-acetic acid is similarly prepared (*Besthorn, Garben*, Ber. **33**, 3439).

DIHYDROXYQUINOLINECARBOXYLIC ACIDS. 2,4-Dihydroxyquinoline-3-carboxylic acid methyl ester, m.p. 204°, from anthranilic acid, malonic ester and sodium ethylate at 150° (*Koller*, Ber. **60**, 1108). The free acid is immediately decarboxylated to 2,4-quinolinediol.

Hydroquinolines

1,2-Dihydroquinolines or Δ^3-dihydroquinolines have been obtained up to the present time only in bimolecular or polymolecular form, by the reduction of quinolines with zinc dust and hydrochloric acid, together with tetrahydroquinolines (*Heller*, Ber. **44**, 2106), and by electrolytic reduction. In this form they cannot be reduced to tetrahydroquinolines, but they are readily oxidized back to the corresponding quinolines with CrO_3, HgO, and the like. **Dihydroquinaldine, dimeric form** $[C_9H_8N(CH_3)]_2$, m.p. 178°. **8-Methyl-1,2-dihydroquinoline**, m.p. 144°. **2,8-Dimethyl-1,2-dihydroquinoline**, m.p. 217°.

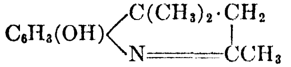
1,2-Dialkyl- and 1,2,2-trialkyl-1,2-dihydroquinolines are formed by the action of alkylmagnesium halides on 1-alkylquinolinium iodides (p. 231). They are monomolecular and are reduced by tin and hydrochloric acid to tetrahydroquinolines (*Freund, Kessler*, J.pr. **98**, 233). **1,2-Dimethyl-** and **1-methyl-2-ethyl-1,2-dihydroquinoline**, b.p. 258° and 266°. **1-Methyl-2-phenyl-1,2-dihydroquinoline**, m.p. 90° (*Meisenheimer, Stotz, Bauer*, Ber. **58**, 2320), is oxidized by $KMnO_4$ to 1-methylbenzoylanthranilic acid. **1,2,2-Trimethyl-2-phenyl-1,2-dihydroquinoline**, b.p. 274°. Dihydroquinolines presumably occur as intermediate products in the *Döbner-Miller* synthesis for quinolines (p. 227), but because of their instability cannot generally be isolated. When the reaction mixture from the condensation of aniline and pyruvic acid is treated with formaldehyde, derivatives of 2-methyl-1,2-dihydrocinchoninic acid, the **hydroglauconic acids**, with the probable structure:



$$CH\left[C_6H_3\begin{matrix}\diagup C(COOH):CH\\ \diagdown NH\text{———}CH(CH_3)\end{matrix}\right]_3$$

are formed. In alkaline solution they are oxidized by the air to **glauconic acids**, blue mordant dyes, which are somewhat similar in structure to the triphenylmethane dyes (Vol. III, p. 525) (*cf. Doebner*, Ber. **31**, 686; **33**, 677).

For *Bz*-**hydroxy-2,3,3-trimethyl-1,2-dihydroquinoline,**



$$C_6H_3(OH)\begin{matrix}\diagup C(CH_3)_2\cdot CH_2\\ \diagdown N\text{═══}CCH_3\end{matrix}$$

from *m*-aminophenol and mesityl oxide, see *v. Pechmann, Schwarz*, Ber. **32**, 3701.

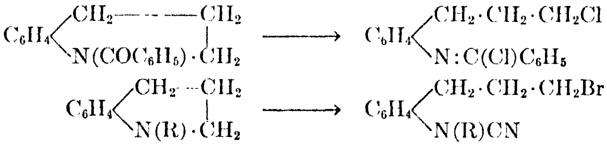
The N-alkyl ethers of the quinolinols (p. 238) are derivatives of *oxodihydroquinolines* or *quinolones*. The quinolone methides are methylenedihydroquinolines.

TETRAHYDROQUINOLINES. When quinoline derivatives are reduced with tin and hydrochloric acid, sodium and alcohol, 3% sodium amalgam (*Ciusa, Barattini*, Gazz. **56**, 131) or hydrogen and nickel at 160–180° (*v. Braun*, Ber. **55**, 3779), 1,2,3,4-tetrahydroquinolines are produced. When quinolines alkylated in the pyridine nucleus are reduced, 5,6,7,8-tetrahydroquinolines in varying amounts are also formed. This is an indication that the point of hydrogen addition is determined by the constitution of the substance hydrogenated (*v. Braun*, Ann. **478, 176**).

Reduction changes the chemical nature of the quinoline derivatives materially. *The tetrahydroquinolines behave like secondary aliphatic-aromatic amines.* With nitrous acid they form N-nitrosoamines, which rearrange readily to 6-nitrosotetrahydroquinolines; with benzenediazonium salts they give diazoamino compounds, which yield 6-azo derivatives by rearrangement, etc. This change in the character of quinoline is similar to that of the indoles on conversion to dihydroindoles (p. 71).

Tetrahydroquinolines are oxidized to quinolines by chromic acid, silver acetate, mercuric nitrate, or iodine [*Tafel*, Ber. **27**, 824; *Schmidt*, Arch. Pharm. **237** (1900), 561].

As in the case of piperidine (p. 220), the piperidine ring of tetrahydroquinoline is opened by treatment of the N-benzoyl derivative with PCl_5, or of the N-alkyl derivatives with cyanogen bromide, derivatives of *o*-propylaniline being formed (*v. Braun*, Ber. **37**, 2921; **42**, 2219):



$$C_6H_4\left\langle\begin{matrix}CH_2\text{------}CH_2\\ N(COC_6H_5)\cdot CH_2\end{matrix}\right. \longrightarrow C_6H_4\left\langle\begin{matrix}CH_2\cdot CH_2\cdot CH_2Cl\\ N{:}C(Cl)C_6H_5\end{matrix}\right.$$

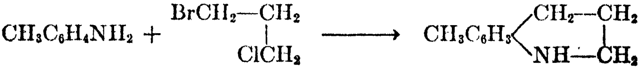
$$C_6H_4\left\langle\begin{matrix}CH_2\text{--}CH_2\\ N(R)\cdot CH_2\end{matrix}\right. \longrightarrow C_6H_4\left\langle\begin{matrix}CH_2\cdot CH_2\cdot CH_2Br\\ N(R)CN\end{matrix}\right.$$

The *Hofmann* decomposition reaction, however, does not apply to the tetrahydroquinolines(*v. Braun*, Ber. **42**, 2533). For the cleavage of the tetrahydroquinoline ring by reduction of the quaternary ammonium salts, see *v. Braun*, Ber **55**, 3803.

1,2,3,4-Tetrahydroquinoline, $C_9H_{11}N$, b.p. 244°, a liquid at ordinary temperatures, is produced by intermoleular alkylation of 2-(γ-chloropropyl)aniline, NH_2-[1]C_6H_4[2]$CH_2CH_2CH_2Cl$ (*v. Braun*, *Steindorff*, Ber. **38**, 583), and by reduction of quinoline and 2- and 4-chloroquinoline with Fe and hydrochloric acid and of carbostyril with sodium and alcohol (*Bamberger*, *Lengfeld*, Ber. **23**, 1142). It is readily dehydrogenated to quinoline with nitrobenzene, iodine, mercuric acetate, or metallic nickel. Further hydrogenation yields hexahydro- and decahydroquinoline (see below). With nitrous acid it forms a nitroso derivative, which rearranges readily to 6-nitrosotetrahydroquinoline, m.p. 124° (*Hofmann*, *Königs*, Ber. **16**, 732). With benzoyl chloride it gives 1-benzoyltetrahydroquinoline, m.p. 75°, and with methyl iodide, **1-methyltetrahydroquinoline, kairoline**, $C_9H_{10}N\cdot CH_3$, b.p. 245°, which, like **kairine**, the hydrochloride of **1-methyl-1,2,3,4-tetrahydroquinolinol-2**, $C_9H_9(OH)N\cdot CH_3$, m.p. 114°, and **thalline**, the sulfate of **6-methoxytetrahydroquinoline**, $C_9H_9(OCH_3)NH$, m.p. 42°, b.p. 283°, acts as a febrifuge. The N-oxide of kairoline has been resolved into optically active components (*Meisenheimer*, Ann. **385**, 134; *cf.* Vol. I, p. 268).

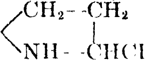
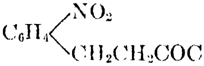
1,2,3,4-Tetrahydroquinoline is converted by oxidation with $KMnO_4$ in acetone solution to 1,1′,2,2′,3,3′,4,4′-octahydro-1,1′-biquinoline, m.p. 142°; this undergoes a benzidine rearrangement when its ethereal solution is shaken with aqueous hydrochloric acid, forming octahydro-6,6′-biquinoline, m.p. 129° (*Wieland*, Ber. **53**, 1336).

1,2,3,4-Tetrahydrotoluquinoline, $CH_3C_6H_3{:}(C_3H_7N)$, b.p. 257°, is prepared by boiling toluidine with 1-bromo-3-chloropropane (*Bamberger*, *Wulz*, Ber. **24**, 2061; *Pinkus*, Ber. **25**, 2805):



$$CH_3C_6H_4NH_2 + \begin{matrix}BrCH_2\text{—}CH_2\\ \quad ClCH_2\end{matrix} \longrightarrow CH_3C_6H_3\left\langle\begin{matrix}CH_2\text{—}CH_2\\ NH\text{—}CH_2\end{matrix}\right.$$

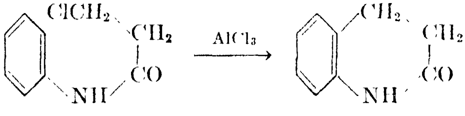
Nitroso derivative, m.p. 51°; benzenediazo-compound, m.p. 99°.

1,2,3,4-Tetrahydroquinaldine,  $C_6H_4\left\langle\begin{matrix}CH_2-CH_2\\ |\\ NH-CHCH_3\end{matrix}\right.$, b.p. 247°, is also formed by the reduction of β-*o*-nitrobenzylacetone,  $C_6H_4\left\langle\begin{matrix}NO_2\\ CH_2CH_2COCH_3\end{matrix}\right.$ (*Jackson,* Ber. **14,** 890). It contains an asymmetric carbon atom and has been resolved into two optically active components by means of its bitartrate and bromocamphorsulfonate (*Ladenburg, Herrmann,* Ber. **41,** 966; *Pope, Read,* J. **97,** 2199).

Several tetrahydroquinolinium bases with two different radicals, such as 1-allyl-1-methyl-1,2,3,4-tetrahydroquinolinium hydroxide, $C_9H_{10}N(CH_3)(C_3H_5)$-OH, and its iodide, have been separated into *optically active nitrogen compounds* by means of the *d*-camphorsulfonates or *d*-bromocamphorsulfonates (*Wedekind,* Ber. **38,** 1840; *Wedekind, Wedekind,* Ber. **40,** 4450; *Wedekind, Maiser,* Ber. **61,** 1364). However, all attempts to resolve 1-methyl-1,2,3,4-tetrahydroquinoline (kairoline), and thereby obtain an optically active compound of trivalent nitrogen, have failed (*Meisenheimer, Angermann, Finn, Vieweg,* Ber. **57,** 1744).

5,6,7,8-Tetrahydroquinoline, b.p. 222°, picrate, m.p. 157°, platinum double salt m.p. 210°, was first prepared by oxidation of the pressure-hydrogenation product of cinchonine over the 5,6,7,8-*tetrahydrocinchoninic acid* (m.p. 242°). It has been synthesized in small yield from 2-hydroxymethylenecyclohexanone and α-cyanoacetamide by a series of reactions (*v. Braun, Lemke,* Ann. **478,** 181). For other ring-syntheses, see *Stobbe,* Ber. **35,** 3978. Reduction with sodium and alcohol converts the 5,6,7,8-tetrahydroquinolines to decahydroquinolines.

The δ-lactams of *o*-aminophenyl fatty acids are *oxo derivatives* of 1,2,3,4-tetrahydroquinoline, *e.g.*, **hydrocarbostyril,** *o*-aminophenylpropionic acid lactam. In accordance with this relationship, hydrocarbostyrils are easily obtained from arylides of the technically produced β-chloropropionic acid by the action of $AlCl_3$ (*Meyer, van Zütphen, Philipps,* Ber. **60,** 858):



Hydrocarbostyril is also prepared by the *Beckmann* rearrangement of 1-indanone oxime.

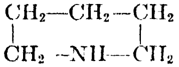
The hydrocarbostyrils decompose when heated with $Ba(OH)_2$ at 150° into *o*-aminophenylpropionic acids (*Meyer, Philipps, Ruppert, Schmitt,* Ber. **61,** 1966).

Hydrocarbostyril (3,4-dihydro-2(1)-quinolone), m.p., 163°, and numerous homologues: *Meyer, van Zütphen, Philipps,* Ber. **60,** 861.

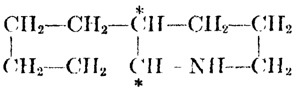
2,3-Dihydro-4(1)-quinolones have been synthesized from N-phenyl-N-(*p*-toluenesulfonyl)-β-aminopropionic acid, $C_6H_5\cdot N(SO_2\cdot C_6H_4\cdot CH_3)\cdot CH_2\cdot CH_2\cdot COOH$, and its homologues with P_2O_5 (*Clemo, Perkin,* J. **127,** 2338).

HEXA- AND DECAHYDROQUINOLINES. When quinoline or tetrahydroquinoline is heated with hydriodic acid and phosphorus at a high temperature, or treated with hydrogen under 110 atm. pressure in the presence of nickel oxide at 240° (*Ipatiew,* Ber. **41,** 992), or when quinoline is hydrogenated in acetic acid solution with colloidal platinum and H_2 at 3 atm. (*Skita, Meyer,* Ber. **45,** 3591) or with platinum black containing oxygen (*Zincke, Eismayer,* Ber. **51,** 767), the benzene ring also adds hydrogen, and decahydroquinoline, together with a little **hexahydroquinoline,** $C_9H_{13}N$, b.p. 226° (*Bamberger, Williamson,* Ber. **27,** 1459), and other products, are formed.

Decahydroquinoline, $C_9H_{17}N$, m.p. 48°, b.p. 204°, a very volatile, strongly alkaline substance, with a stupefying odor like that of coniine. While the tetrahydroquinoline behaves like a mixed aliphatic-aromatic amine, decahydroquinoline has the properties of an aliphatic secondary amine; it is the *piperidine of the quinoline series:*



Piperidine



Decahydroquinoline

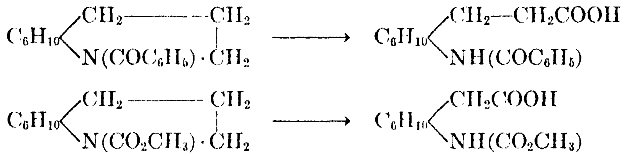
On total hydrogenation (by the method of *Sabatier*, or in glacial acetic acid with Pt and H_2) decahydroquinoline is obtained in two stereoisomeric forms, *cis*- and *trans*-, in reference to the union of the two rings (analogous to *cis*- and *trans*-decalin) [*Hückel, Stepf*, Ann. **453**, 163; *Fuiise*, Sci. Papers Inst.Phys.Chem. Research Tokyo 8 (1928), 161]:

Trans-, m.p. 48.5°, b.p. 201°; hydrochloride, m.p. 275°; chloroaurate, m.p. 124°.

Cis-, liquid, b.p. 205°; hydrochloride, m.p. 226°; chloroaurate, m.p. 157°.

Decahydroquinoline contains two asymmetric carbon atoms (*); this has been verified by resolution with the help of *d*-bromocamphorsulfonic acid.

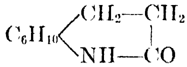
When the benzoyl or urethan derivative is oxidized, the decahydroquinoline ring suffers the same type of fission as in the case of piperidine (p. 220): the products are *o*-benzoylaminocyclohexanepropionic acid and *o*-carbomethoxy-aminocyclohexaneacetic acid:



$$C_6H_{10}\left\langle\begin{array}{l} CH_2 - - - CH_2 \\ \qquad\qquad\quad | \\ N(COC_6H_5)\cdot CH_2 \end{array}\right. \longrightarrow C_6H_{10}\left\langle\begin{array}{l} CH_2 - CH_2COOH \\ NH(COC_6H_5) \end{array}\right.$$

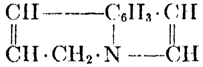
$$C_6H_{10}\left\langle\begin{array}{l} CH_2 - - - CH_2 \\ \qquad\qquad\quad | \\ N(CO_2CH_3)\cdot CH_2 \end{array}\right. \longrightarrow C_6H_{10}\left\langle\begin{array}{l} CH_2COOH \\ NH(CO_2CH_3) \end{array}\right.$$

The free *o*-aminocyclohexanepropionic acid anhydrizes to **octahydrocarbostyril** (*Bamberger, Williamson*, Ber. **27**, 1458):



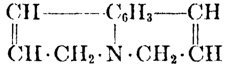
$$C_6H_{10}\left\langle\begin{array}{l} CH_2 - CH_2 \\ \qquad\quad | \\ NH - CO \end{array}\right.$$

Condensed derivatives of hydroquinolines include the **julole** and **lilole** derivatives, which are derived from the hypothetical parent substances:



$$\begin{array}{lcl} CH - - - & C_6H_3\cdot & CH \\ \| & | & \| \\ CH\cdot CH_2\cdot & N - - & CH \end{array}$$

Lilole
4-Pyrrolo[3,2,1-*ij*]quinoline



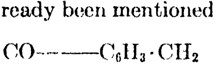
$$\begin{array}{lcl} CH - - - & C_6H_3 - - & CH \\ \| & | & \| \\ CH\cdot CH_2\cdot & N\cdot & CH_2\cdot CH \end{array}$$

Julole
3,5-Dihydrobenzo[*ij*]quinolizine

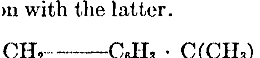
Lilole is a combination of a quinoline ring with a pyrrole ring, or a pyridine ring with an indole ring, and julole is a combination of a quinoline ring with a pyridine ring.

Methyllilolidinedione, 2-*methyl*-1,2-*dihydro*-4-*pyrrolo*[3,2,1-*ij*]*quinoline*-4,6(5)-*dione* (I) is prepared from malonic acid ester with dihydromethylindole (p. 71) and has already been mentioned in connection with the latter.

(I)



$$\begin{array}{lcl} CO - - - & C_6H_3\cdot & CH_2 \\ | & | & | \\ CH_2\cdot CO\cdot & N - - & CHCH_3 \end{array}$$



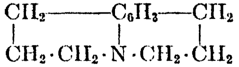
$$\begin{array}{lcl} CH_2 - - - & C_6H_3\cdot & C(CH_3) \\ | & | & \| \\ CH_2\cdot CH_2\cdot & N\cdot CO\cdot & CH \end{array}$$

(II)

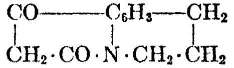
Methyloxojuloline, 1-*methyl*-6,7-*dihydrobenzo*[*ij*]*quinolizin*-3(5)-*one* (II), m.p. 130°, is obtained from tetrahydroquinoline with acetoacetic ester (*Reissert*, Ber. **24**, 845).

Julolidine, 1,2,3,5,6,7-*hexahydrobenzo*[*ij*]*quinolizine* (III),

(III)



$$\begin{array}{lcl} CH_2 - - - & C_6H_3 - - & CH_2 \\ | & | & | \\ CH_2\cdot CH_2\cdot & N\cdot & CH_2\cdot CH_2 \end{array}$$

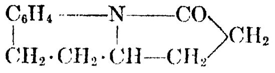


$$\begin{array}{lcl} CO - - - & C_6H_3 - - & CH_2 \\ | & | & | \\ CH_2\cdot CO\cdot & N\cdot & CH_2\cdot CH_2 \end{array}$$

(IV)

m.p. 40°, is produced when tetrahydroquinoline is boiled with 1 mol of 1-bromo-3-chloropropane, or aniline with 2 mols of 1-bromo-3-chloropropane (*Pinkus*, Ber. **25**, 2801). Both julole derivatives are bases, but **julolidinedione** (IV), 6,7-*dihydrobenzo*[*ij*]*quinolizine*-1(2),3(5)-*dione*, from tetrahydroquinoline with malonic ester, has only acid properties.

A similar ring system is contained in **tetrahydroquinoline-2-propionic acid lactam,** 3,3*a*,4,5-*tetrahydropyrrolo*[*a*]*quinolin*-1(2)-*one*, m.p. 116°:



$$\begin{array}{l} C_6H_4\text{——}N\text{——}CO\diagdown \\ \quad | \qquad\quad | \qquad\qquad\quad >CH_2 \\ CH_2\cdot CH_2\cdot CH\text{—}CH_2\diagup \end{array}$$

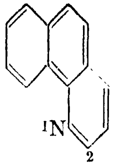
The lactam or the free acid is formed by reduction of 2-quinolineacrylic acid (p. 233) with Na and alcohol. In many respects it resembles *strychnine* (p. 379) (*Koenigs*, Ber. **33**, 218). *Cf.* also piperolidone (p. 224).

Condensed Quinolines

The quinoline syntheses from aniline or its homologues according to *Skraup* or *Döbner-Miller* (p. 227) can also be carried out with naphthylamines, aminoanthracenes, aminoanthraquinones, and the like; higher condensed ring systems containing a quinoline nucleus are produced. The angular union of the pyridine ring is far more common than the linear arrangement, although the latter does occur in products from tetrahydronaphthalene derivatives, *e.g.*, *Bz-tetrahydro-2-naphthylamine* (*v. Braun*, *Gruber*, Ber. **55**, 1710; *Lindner*, *Staufer*, Mo. **46**, 231), since the valence distribution in these cases is more favorable to the linear condensation.

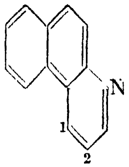
The two naphthylamines give benzo[*h*]quinoline (α-naphthoquinoline) (I) and benzo[*f*]quinoline (β-naphthoquinoline) (II), and aminoanthracene yields naphtho[2,3-*f*]quinoline (β-anthraquinoline) (IV):

(I)



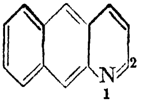
Benzo[*h*]quinoline
(α-Naphthoquinoline)

(II)



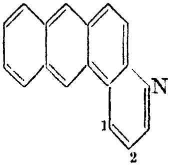
Benzo[*f*]quinoline
(β-Naphthoquinoline)

(III)



Benzo[*g*]quinoline
(Anthrapyridine)

(IV)

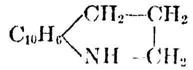


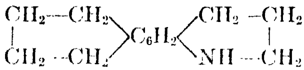
Naphtho[2,3-*f*]quinoline
(β-Anthraquinoline)

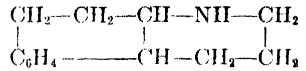
Benzo[*h*]quinoline, *α-naphthoquinoline*, m.p. 52°, b.p. 338°. **Benzo[*f*]quinoline**, *β-naphthoquinoline*, m.p. 93°, b.p. 210° (22 mm.). The latter is also prepared from 1-bromo- or 1-nitro-2-naphthylamine. With $KMnO_4$ the benzoquinolines are oxidized to two phenylpyridinedicarboxylic acids (p. 205). By amination and subsequent oxidation with $KMnO_4$, benzo[*h*]quinoline is converted to 7,8-quinolinedicarboxylic acid, and benzo[*f*]quinoline to 5,6-quinolinedicarboxylic acid (*Hepner*, Mo. **27**, 1045; for the numbering of the quinoline ring, see p. 226). **3-Methylbenzo[*f*]quinoline**, *β-naphthoquinaldine*, m.p. 82°, from 2-napthylamine by the *Döbner-Miller* synthesis [*Browning*, *Cohen*, *Ellingworth*, *Gulbransen*, Proc.Roy.Soc.London **B100** (1926), 293]. **Indeno[1,7-*gh*]quinoline**, *acenaphthoquinoline*, m.p. 62°, from 5-aminoacenaphthene (*Stewart*, J. **127**, 1331).

3-Benzo[*f*]quinolinol, *2-hydroxy-β-naphthoquinoline*, m.p. over 280°, by heating benzo[*f*]quinoline with caustic potash at 280–300° (Ger. Pat. 406208, 1922).

The pyridine ring is hydrogenated first when the benzoquinolines are reduced with tin and hydrochloric acid:


(V)


(VI)


(VII)

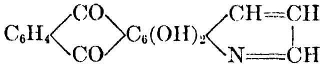
1,2,3,4-**Tetrahydrobenzo**[*h*]**quinoline** (V), m.p. 46°, and 1,2,3,4-**tetrahydrobenzo**[*f*]**quinoline**, m.p. 63°, behave like alkylated 1- and 2-naphthylamines. Tetrahydro-1-naphthylamine according to the *Döbner-Miller* synthesis gives *tetrahydrobenzo*[*h*]*quinoline*, in which the outside benzene ring is the first to be hydrogenated on reduction (*Lindner, Siegel,* Mo. **46**, 225). Reduction with sodium and boiling amyl alcohol gives 1,2,3,4,7,8,9,10-**octahydrobenzo**[*h*]-**quinoline** (VI), m.p. 48°, b.p. 216° (37 mm.), and the corresponding benzo[*f*]-quinoline derivative, m.p. 60°, b.p. 325°, in which both the pyridine and the outside benzene ring are hydrogenated, causing the products to have the nature of alkylated anilines. From benzo[*f*]quinoline there is simultaneously formed an isomeric *octahydro-(β)-naphthoquinoline,* 1,2,3,4,4a,5,6,10a-**octahydrobenzo**[*f*]-**quinoline** (VII), m.p. 91°, b.p. 321°, in which the middle benzene ring is hydrogenated; this compound corresponds to decahydroquinoline (p. 245) and has the properties of a piperidine.

Quino[8,7-*h*]**quinoline**, 1,5-**naphthodiquinoline**, $C_{16}H_{10}N_2$, m.p. 217°, from 1,5-naphthalenediamine, glycerol and H_2SO_4 (*Finger, Spitz,* J.pr. **79**, 445).

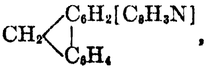
Benzo[*g*]**quinoline**, *α-anthrapyridine,* m.p. 114°, b.p. 200-205° (14 mm.) (formula III, p. 247), from 1,2,3,4-tetrahydro-2-naphthylamine over its tetrahydro compound by dehydrogenation with lead oxide. Oxidation with CrO_3 converts it to **benzo**[*g*]**quinoline-5,10-quinone**, *anthrapyridinequinone,* m.p. 280°, which corresponds to anthraquinone; this quinone can also be obtained synthetically from quinolinic anhydride and benzene in the presence of $AlCl_3$ (*v. Braun, Gruber,* Ber. **55**, 1710). 6,9-**Dihydroxybenzo**[*g*]**quinoline-5,10-quinone**, 5,8-*dihydroxyanthrapyridinequinone,* m.p. 237°, red needles, from quinolinic acid and hydroquinone, corresponds to quinizarin [*Niementowski, Frühling, Joszt,* Roczniki Chem. **7** (1927), 218].

Naphtho[2,3-*f*]**quinoline**, *β-anthraquinoline* $C_{17}H_{11}N$, m.p. 170°, b.p. 446°; its solutions show intense blue fluorescence. It is oxidized by CrO_3 to **naphtho**-[2,3-*f*]**quinoline-7,12-quinone**, *β-anthraquinonequinoline,* m.p. 185°, whose dihydroxy derivative is alizarin blue (*Graebe,* Ann. **201**, 349). For 3-**phenylnaphtho**[2,3-*f*]**quinoline**, *2-phenyl-β-anthraquinoline,* m.p. 285°, see *Musajo,* Gazz. **59**, 74. **Naphtho**[2,3-*h*]**quinoline-7,12-quinone**, *α-anthraquinonequinoline,* m.p. 169°, can be prepared from 1-aminoanthraquinone, glycerol and H_2SO_4 (Ger. Pat. 189234, 1905), although 2-aminoanthraquinone under the same conditions forms benzanthrone (Vol. III, p. 696) and 13-**phenanthro**[10,1-*fg*]**quinoline**, *benzanthronequinoline,* $C_{20}H_{11}ON$, m.p. 251°; the latter compound, like benzanthrone, is converted by fusion with alkali to a blue-violet dye of outstanding fastness, **cyananthrene** (*Bally,* Ber. **38**, 194; Ger. Pat. 171939, 1904).

ALIZARIN BLUE, 5,6-**dihydroxynaphtho**[2,3-*f*]**quinoline-7,12-dione**, *dihydroxyanthraquinonequinoline:*

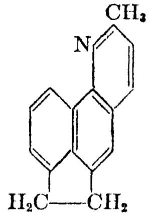


m.p. 270°, metallic blue-violet needles, is obtained from 2-nitro- or 2-aminoalizarin with glycerol and H_2SO_4 (*Brunner, Chuard,* Ber. **18**, 445; *Knueppel,* Ber. **29**, 708) (*cf.* Vol. III, p. 663). It forms salts with both acids and bases. It is marketed in the form of a violet paste and its method of application is similar to that of alizarin. In the form of the bisulfite derivative it is called alizarin blue S. Since it is decolorized by reducing agents (zinc dust, grape sugar) and regenerated by exposure to the air, it is suitable for *vat dyeing*. By treatment with H_2SO_4 several hydroxyl groups can be introduced into alizarin blue. The products are mixtures of sulfonic acids of tri-, tetra-, and pentahydroxy derivatives of alizarin blue, and are known as alizarin blue-green, alizarin green and alizarin indigo blue (*Graebe, Philips,* Ann. **276**, 21).

11-Indeno[2,1-*f*]**quinoline**, ***fluorenequinoline***,  $CH_2\left\langle\begin{matrix}C_6H_2[C_9H_3N]\\ |\\ C_6H_4\end{matrix}\right.$, **m.p. 133°,**

and **dibenzo[*f,h*]quinoline,** 9,10-*phenanthroquinoline,* $C_{17}H_{11}N$, m.p. 174°, are prepared from 2-aminofluorene and 9-aminophenanthrene by the *Skraup* synthesis (*Diels, Staehlin,* Ber. **35,** 3275; *Herschmann,* Ber. **41,** 1998).

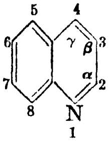
9-**Methylindeno**[1,7-*gh*]**quinoline,** 2-*methylacenaphtha*-5,6-*pyridine:*



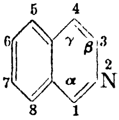
m.p. 131°, from 5-aminoacenaphthene and paraldehyde (*Nair, Simonsen,* J. **1926,** 3140).

(c) Isoquinolines

While in quinoline the carbon atoms in the 2- and 3-positions are common to the benzene and the pyridine rings, in isoquinoline the carbon atoms in the 3- and 4-positions are shared. Isoquinoline is therefore also called 3,4-benzopyridine. The nitrogen atom in the isoquinoline ring is separated from the benzene nucleus by a methine group.



Quinoline

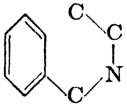


Isoquinoline

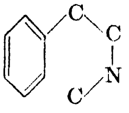
The constitution of isoquinoline is evident from its oxidation to 3,4-pyridinedicarboxylic acid and from its various syntheses.

In its reactions isoquinoline resembles quinoline. It occurs with quinoline in coal tar (*Hoogewerff, van Dorp,* 1885, *cf. Weissgerber,* Ber. **47,** 3175) and is the mother substance of a series of important alkaloids in the group of opium bases, such as *papaverine, narcotine, hydrastine,* and *apomorphine* (pp. 359 *ff.*).

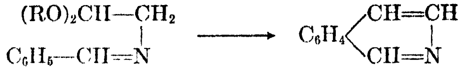
Synthesis of Isoquinoline Derivatives.—(*1*) Isoquinoline is obtained by ring-closure of benzene derivatives with the grouping:



or

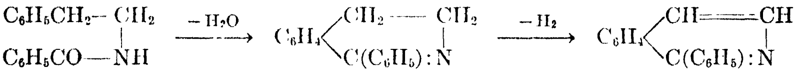


(*a*) Isoquinoline is prepared from β-benzylideneaminoethyl acetal or benzylaminoacetaldehyde by warming with H_2SO_4 (*Pomeranz,* Mo. **15,** 299; *Hantzsch, Urbahn,* Ber. **28,** 764); or with H_2SO_4 and arsenic acid (*Rügheimer, Schön,* Ber. **42,** 2374); this method has but a limited range of applicability (*cf. Staub,* Helv. **5,** 888):

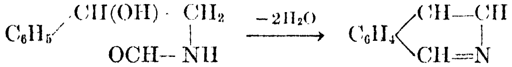


β-Benzylideneaminoethyl acetal Isoquinoline

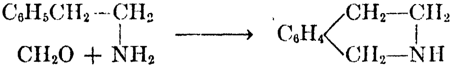
(*b*) A more important method is that derived from the second grouping above, consisting in the elimination of water from acylated phenethylamines by means of P_2O_5 in boiling toluene, xylene (*Späth, Polgar*, Mo. **51,** 192) or tetralin solution (*Späth, Berger, Kuntara*, Ber. **63,** 134). The dihydroisoquinolines so formed are oxidized to isoquinolines with $KMnO_4$ in acid solution or by catalytic dehydrogenation (*Späth, Polgar*, Mo. **51,** 193; *Späth, Berger, Kuntara*, Ber. **63,** 134; *Pictet, Kay*, Ber. **42,** 1973; *Decker, Kropp*, Ber. **42,** 2075; for a modification of this method, see *v. Braun, Blessing, Cahn*, Ber. **57,** 908; Ger. Pat. 399805, 1920, Frdl. **XIV,** 1313):



Acylated α-hydroxyphenethylamines of the formula $C_6H_5CH(OH)$-CH_2NHCOR (*Pictet, Gams*, Ber. **43,** 2384) or the corresponding ethers [*Rosenmund, Nothnagel, Riesenfeldt*, Ber. **60,** 392; *Mannich, Walther*, Arch. Pharm. **265** (1927), 1] give isoquinolines directly when treated with P_2O_5:

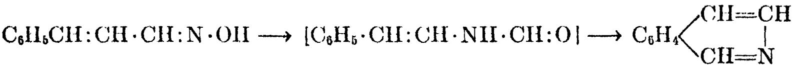


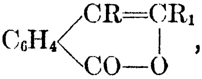
When phenethylamines are condensed with aldehydes, tetrahydroquinolines are formed (*Pictet, Spengler*, Ber. **44,** 2030):



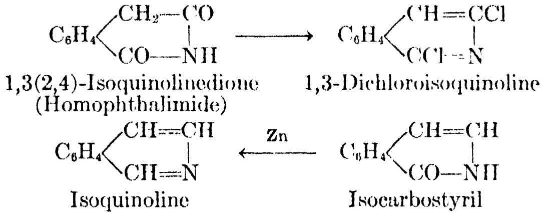
Method (*b*) can be used for the preparation of complicated isoquinoline compounds, such as those of the type of berberine (*Chakravarti, Haworth, Perkin*, J. **1927,** 2265; *Haworth, Perkin, Pink*, J. **127,** 1709) and of apomorphine (*Robinson, Shinoda*, J. **1926,** 2198).

(*c*) Isoquinoline is formed from cinnamaldoxime and from benzylideneacetoxime by heating with P_2O_5, a *Beckmann* rearrangement taking place (*Goldschmidt*, Ber. **27,** 2795; **28,** 818):



(2) In lactones of the formula , called isocoumarins (p. 184), the linking oxygen can be exchanged for an NH-group by means of cold aqueous ammonia, forming isoquinolones or isocarbostyrils, which are converted into isoquinolines by successive treatment with PCl_5 and HI and phosphorus or with zinc dust. Similar treatment transforms 1,3(2,4)-isoquinolinedione (homophthalimide) and its homologues into isoquinolines (*Le Blanc*, Ber. **21,**

2290; *Bamberger, Kitschelt,* Ber. **25,** 1138; *Zincke,* Ber. **25,** 1493; *Gabriel, Neumann,* Ber. **25,** 3563; *Bamberger, Lodter,* Ber. **26,** 1842):



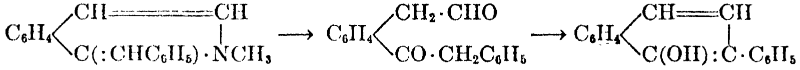
Isoquinoline, m.p. 24° [*Frank, Vollmer,* Braunkohle **23** (1924), 505], b.p. 240.5° (763 mm.), d 1.096, is quite similar to quinoline. It is obtained from the crude quinoline of coal tar in 4% yield (*Forsyth, Kelly, Pyman,* J. **1927,** 1659) by fractional crystallization of the sulfates, or by gradual concentration of the isoquinoline by shaking with H_2SO_4, due to its greater basicity (*Weissgerber,* Ber. **47,** 3175; *Harris, Pope,* J. **121,** 1029). It is prepared by the methods given above and also by distillation of N-benzylideneëthylamine, C_6H_5-CH:N·CH_2CH_3, through an incandescent tube (*Pictet, Popovici,* Ber. **25,** 734) and in smaller yield by distillation of N-methylphthalimidine (*Pictet,* Ber. **38,** 1949) and of yohimbine (*Winterstein, Walter,* Helv. **10,** 577) with zinc dust. Oxidation of isoquinoline with $KMnO_4$ produces both *phthalic acid,* by destruction of the pyridine nucleus, and *cinchomeronic acid* (3,4-pyridinedicarboxylic acid), by destruction of the benzene nucleus. The alkyl halide addition products of isoquinoline give alkylated phthalimides, $C_6H_4(CO)_2NR$, when oxidized.

Isoquinoline 2-oxide, hydrate, m.p. 98° (*Meisenheimer,* Ber. **59,** 1848). *Isoquinoline picrate,* m.p. 223°. *Chloroplatinate,* $((C_9H_8N)_2PtCl_6 + 2 H_2O$, m.p. 260°. 2-*Methylisoquinolinium iodide,* $C_9H_7N \cdot ICH_3$, m.p. 159°; the 2-*ethyl iodide,* m.p. 148°. The 2-alkylisoquinolinium iodides react like the pyridinium and quinolinium iodides (p. 201 and p. 230). With sodium hydroxide solution they first form the unstable isoquinolinium hydroxides, which rearrange to 1-hydroxydihydroisoquinolines; these are oxidized to 2-alkyl-1-isoquinolones by alkaline potassium ferricyanide solution. With alkylmagnesium halides they give 1,2-dialkyldihydroisoquinolines (p. 254). For the action of cyanogen bromide and hydrocyanic acid, see *Mumm, Herrendorfer,* Ber. **47,** 764, and *Shimidzu,* J.pharm. Soc. Japan **1926,** No. 537, 94. Nitration of isoquinoline yields a *Bz*-**nitroisoquinoline,** m.p. 110° (*Edinger,* J.pr. **53,** 375). 1,3-**Dioxolo**[*g*]**isoquinoline,** 6,7-*methylenedioxyisoquinoline,* $(CH_2O_2)C_6H_2(C_3H_3N)$, m.p. 124°, from piperonalaminoacetal; its methyl iodide addition product reduces to hydrohydrastinine, 6-methyl-5,6,7,8-tetrahydro-1,3-dioxolo-[*g*]isoquinoline (p. 369; *Fritsch,* Ann. **286,** 1).

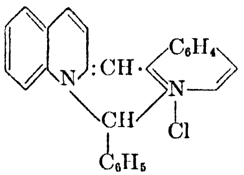
8-**Methyl**- and 6-**methylisoquinoline,** b.p. 258°, and m.p. 83°, b.p. 264°, are prepared from *β*-*o*- and *p*-methylbenzylideneaminoethyl acetal (*Pomeranz,* Mo. **18,** 1).

1-**Methylisoquinoline,** b.p. 245° (728 mm.), sulfate m.p. 247°, is obtained from (*α*-methylbenzylidene)aminoethyl acetal with H_2SO_4 (*Pomeranz,* Mo. **15,** 299) and from N-acetyl-*β*-hydroxyphenethylamine with P_2O_5 (*Pictet, Gams,* Ber. **43,** 2389) and is apparently identical with the methylisoquinoline from *papaveroline* (p. 365) (*Krauss,* Mo. **11,** 350). 3-**Methylisoquinoline,** m.p. 68°, b.p. 246° (761 mm.), is formed from methylisocarbostyril (*Gabriel, Neumann,* Ber. **25,** 3563) by distillation with zinc dust (see above). 4-**Methylisoquinoline,** b.p. 256°, from dimethylhomophthalimide by distillation with zinc dust (*Le Blanc,* Ber. **21,** 2300). 3-**Ethylisoquinoline,** $C_9(C_2H_5)H_6N$, b.p. 256°, and 3-**phenylisoquinoline,** $C_9(C_6H_5)H_6N$, m.p. 104°, are prepared from ethyl- and phenylisocarbostyril (see above) (*Gabriel, Neumann*, Ber. **25**, 3573; *Damerow*, Ber. **27**, 2237). **1-Phenylisoquinoline**, m.p. 93°, from benzohydrylideneaminoacetal $(C_6H_5)_2C:NCH_2CH(OC_2H_5)_2$ with H_2SO_4 (*Pomeranz*, Mo. **18**, 1), from N-benzoyl-β-hydroxyphenethylamine with P_2O_5 (*Pictet, Gams*, Ber. **43**, 2388; *Rosenmund, Nothnagel, Riesenfeldt*, Ber. **60**, 392) and from its dihydro derivative with $KMnO_4$ (*Pictet, Kay*, Ber. **42**, 1976).

4-**Benzylisoquinoline**, m.p. 118°, b.p. 238° (23 mm.), is formed together with a little 3-**benzylisoquinoline**, m.p. 104°, b.p. 311° (23 mm.), when tetrahydroisoquinoline (p. 254) is heated with benzaldehyde; 4-benzylisoquinoline yields pyridine-3,4,5-tricarboxylic acid on oxidation. 1-**Benzylisoquinoline**, m.p. 55°, b.p. 228° (23 mm.), which is the parent compound of several alkaloids (*cf.* papaverine, p. 365; *Rügheimer*, Ber. **33**, 1719; Ann. **328**, 326; *Rügheimer, Friling*, Ann. **326**, 261), is obtained from isoquinoline and benzyl alcohol by heating, from N-phenacetyl-β-hydroxyphenethylamine with P_2O_5 (*Pictet, Gams*, Ber. **43**, 2387) and from its dihydro derivative (*Pictet, Kay*, Ber. **42**, 1978). It oxidizes to pyridine-2,3,4-tricarboxylic acid. Its methyl iodide addition product is converted by aqueous sodium hydroxide, not to the hydroxydihydro base (see above), but, by elimination of water, to the yellow **2-methyl-1-benzylidene-1,2-dihydroisoquinoline**, which is also produced by the action of $C_6H_5CH_2MgCl$ on 2-methyl-1(2)-isoquinolone (p. 253), and which regenerates 2-methyl-1-benzylisoquinolinium iodide when treated with HI (*Decker, Pschorr*, Ber. **37**, 3396). When the latter compound is digested a longer time with aqueous sodium hydroxide, methylamine is eliminated, and 2-*phenyl*-1-*naphthol* results, a reaction which can be explained only by assuming that the 2-methyl-1-benzylidenedihydroisoquinoline originally formed suffers a ring-fission (*Decker*, Ann. **362**, 305):



Quinoline red (or isoquinoline red) is obtained by the action of benzotrichloride on a mixture of isoquinoline and quinaldine (p. 232). For its constitution (14-chloro-15-phenyl-14,15-dihydropyrimido[1,6-*a*, 3,4-*a*′]diquinoline, see formula) and the reaction mechanism of its preparation, see *Vongerichten, Hofmann*, Ber. **45**, 3447; *Scheibe*, Ber. **54**, 786; *Scheibe, Fischer*, Ber. **59**, 502).



It is a red dye which, like the cyanines (p. 234), has the property of making photographic plates orthochromatic.

Isoquinolines halogenated in the pyridine nucleus are prepared from isocarbostyrils (see below) and homophthalimides with PCl_5. Chlorine atoms in the 1-position possess the same reactivity as the chlorine atoms in the 2- or 4-position of quinoline (p. 235).

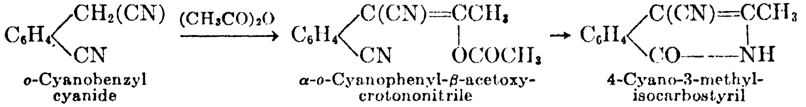
1-**Chloroisoquinoline**, m.p. 38°, b.p. 275°, from isocarbostyril with $POCl_3$ (*Gabriel, Colman*, Ber. **33**, 985). 3-**Chloroisoquinoline**, m.p. 48°, b.p. 281°, results from the partial reduction of 1,3-dichloroisoquinoline, m.p. 122°, b.p. 306°, which is prepared from homophthalimide with $POCl_3$ (*Gabriel*, Ber. **19**, 2355). 1,4-**Dichloroisoquinoline**, m.p. 89°, from hydroxyisocarbostyril with $POCl_3$ (p. 253), together with 1-**chloro-4-isoquinolinol**, m.p. 196° (*Gabriel, Colman*, Ber. **33**, 986). 1-**Chloro-3-methyl-** and 1-**chloro-3-phenylisoquinoline**, m.p. 36° and 77°, from the corresponding isocarbostyrils; the latter reacts with aniline to give 1-*anilino*-3-*phenylisoquinoline*, $C_9H_5(NHC_6H_5)N$, m.p. 126° (*Ephraim*, Ber. **25**, 2709).

Sulfonic acids of isoquinoline are formed by the action of fuming sulfuric acid, the preferred points of entry being the 5- and 8-positions. The 8-**sulfonic acid** so prepared can be converted to 8-isoquinolinol by alkali fusion (*Weissgerber*, Ber. **47**, 3180).

AMINOISOQUINOLINES. When isoquinoline is treated with sodium amide according to the method used in the pyridine and quinoline series, 1-aminoisoquinoline is obtained [*Tschitschibabin*, *Oparina*, J.Russ.Phys.Chem.Soc. **50** (1918), 543].

1-Aminoisoquinoline, m.p. 123°, picrate m.p. 290°, when diazotized and boiled, gives isocarbostyril (see below).

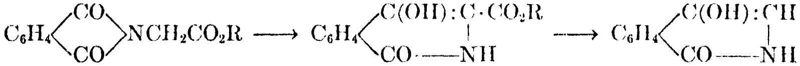
ISOQUINOLINOLS, ISOCARBOSTYRILS. The hydroxyl derivatives of isoquinoline are prepared from the isocoumarins with NH_3 (p. 184). Another more general synthesis consists in the treatment of the reaction products of *o*-cyanobenzyl cyanide and carboxylic acid anhydrides with alkali:



o-Cyanobenzyl cyanide — *α-o*-Cyanophenyl-*β*-acetoxy-crotononitrile — 4-Cyano-3-methyl-isocarbostyril

The alkylcyanoisocarbostyrils so obtained lose the cyano group when treated with concentrated sulfuric acid, forming 3-alkylisocarbostyrils (*Gabriel*, *Posner*, Ber. **27**, 827; *Damerow*, Ber. **27**, 2232; *Harper*, Ber. **29**, 2543).

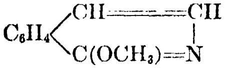
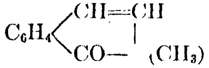
The rearrangement of phthalimido-fatty acid esters by means of sodium alcoholate serves for the preparation of 1,4-isoquinolinediols or 4-hydroxyisocarbostyrils (*Gabriel*, *Colman*, Ber. **33**, 980; *Findeklee*, Ber. **38**, 3542):



The resulting 1,4-dihydroxyisoquinoline-3-carboxylic acid esters are easily decarboxylated, and the 1,4-dihydroxy compounds can be reduced to isocarbostyrils.

As in the case of carbostyrils, alkyl ethers of both the hydroxyl and the keto form of isocarbostyrils can be obtained. The former are usually prepared from the 1-chloroisoquinolines with sodium alcoholates, and the latter from the isocarbostyrils with alkyl iodides or from 2-alkylisoquinolinium iodides with aqueous sodium hydroxide and potassium ferricyanide.

Isocarbostyril, 1-*isoquinolinol*, 1(2)-*isoquinolone*, m.p. 207° [*Tschitschibabin*, *Oparina*, J. Russ. Phys.Chem.Soc. **50** (1918), 543], prepd. from isocoumarin with NH_3, from isocarbostyrilcarboxylic acid, $C_9H_6ON\cdot COOH$, m.p. 320° (dec.), the product of the reaction of isocoumarincarboxylic acid with NH_3, by decarboxylation, and from 1-aminoisoquinoline (see above) by diazotization and digestion. **1-Methoxyisoquinoline** (I), b.p. 240°, is prepared from the Ag-salt of isocarbostyril with methyl iodide. The isomeric **2-methyl-1(2)-isoquinolone** (II), m.p.

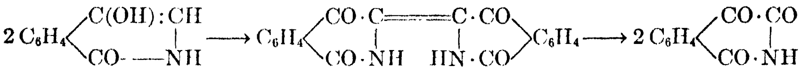
(I)  (II) 

54° (40°: *Decker*, J.pr. **47**, 28; *Bamberger*, *Frew*, Ber. **27**, 205), from isocarbostyril with methyl iodide and alkali (*Fernau*, Mo. **14**, 59) and from methylisoquinolinium iodide with alkaline potassium ferricyanide (p. 251). Other N-alkylisoquinolones are formed by the action of primary amines on isocoumarin (*Bamberger*, *Frew*, Ber. **27**, 198) or its carboxylic acid. **3-Methylisocarbostyril,** m.p. 211°; **3-ethylisocarbostyril,** m.p. 141°; **3-isopropylisocarbostyril,** m.p. 186° (*Lehmkuhl*, Ber. **30**, 892). **3-Phenylisocarbostyril,** *isobenzalphthalimidine*, m.p. 197°, from isobenzalphthalide with NH_3 (*Gabriel*, Ber. **18**, 2448; *Damerow*, Ber. **27**, 2237).

5,6,7-Trihydroxy-4-methylisocarbostyril, $C_6H(OH)_3:[C_3H_2(CH_3)ON]$, is obtained from the corresponding isocoumarin derivative, which is formed from gallacetol, $C_6H_2(OH)_3\cdot CO\cdot O\cdot CH_2COCH_3$, with concentrated sulfuric acid (*Fritsch*, Ber. **26**, 419).

1-Hydroxyisoquinoline-3-carboxylic acid, m.p. 319° (dec.).

4-Hydroxyisocarbostyril, 1,4-*isoquinolinediol*, is prepared by saponification of **1,4-dihydroxyisoquinoline-3-carboxylic acid ester,** m.p. 222°, the product of the rearrangement of N-carbethoxymethylphthalimide, $C_6H_4(CO)_2NCH_2COOC_2H_5$ (see p. 254). The hydroxyisocarbostyril is reduced by hydriodic acid to isocarbostyril, and is oxidized, similarly to indoxyl, to a ring-homologue of indigo, **carbindigo**, a vermilion powder. As indigo is oxidized to isatin, so carbindigo is oxidized by fuming nitric acid to phthalonimide, tetrahydroisoquinoline-1,3,4-trione, which can also be obtained directly by oxidation of hydroxyisocarbostyril with the same reagent:



$$2\,C_6H_4\left\langle\begin{array}{l}C(OH):CH\\ \quad\quad\;\;|\\ CO\text{—}NH\end{array}\right. \longrightarrow C_6H_4\left\langle\begin{array}{l}CO\cdot C\text{===}C\cdot CO\\ \quad\;\;|\quad\quad\;\;|\\ CO\cdot NH\;\;HN\cdot CO\end{array}\right\rangle C_6H_4 \longrightarrow 2\,C_6H_4\left\langle\begin{array}{l}CO\cdot CO\\ \quad\quad|\\ CO\cdot NH\end{array}\right.$$

With sodium methylate and methyl iodide hydroxycarbostyril gives **4-methoxyisocarbostyril**, m.p. 171°. With benzaldehyde and with phthalic anhydride it condenses with elimination of water, and with phthalonimide (see above) it forms carbindigo (*Gabriel, Colman*, Ber. **35**, 2421).

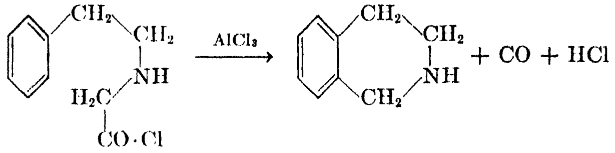
3-Methyl-, 3-**ethyl-**, and **3-phenyl-4-hydroxyisocarbostyril** are prepared from N-carbethoxyethyl-, N-carbethoxypropyl-, and N-(phenylcarbethoxymethyl)-phthalimide by rearrangement and fission (see p. 253) (*Ulrich*, Ber. **37**, 1685; *Bülow, Deiglmayr*, Ber. **37**, 1791).

CARBOXYLIC ACIDS. Isoquinoline-1-carboxylic acid, m.p. 162°, has been obtained from its nitrile (*Zincke, Krollpfeiffer*, Ann. **408**, 338; *Reissert*, Ber. **38**, 3427). **6,7-Dimethoxyisoquinoline-1-carboxylic acid** is formed in the oxidation of *papaverine* with $KMnO_4$.

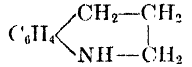
HYDROISOQUINOLINES. (*1*) **Dihydroisoquinolines** are synthesized from acylated phenethylamines with P_2O_5, PCl_5, and $POCl_3$ (p. 250) (*Pictet, Kay*, Ber. **42**, 1973) (for a variation of this method, see Ger. Pat. 399805, 1920, Frdl. **XIV**, 1313), and from 2-alkylisoquinolinium iodides by treatment with alkylmagnesium halides (*Freund, Bode*, Ber. **42**, 1750). In the first case 3,4-, and in the second case, 1,2-dihydroisoquinolines are formed. The dihydroisoquinolines can be converted to the corresponding isoquinolines by $KMnO_4$ in acid solution or by catalytic dehydrogenation (Pd-black, 190°; *Späth, Berger, Kuntara*, Ber. **63**, 134). **1-Methyl-3,4-dihydroisoquinoline**, b.p. 236°; **1-phenyl-3,4-dihydroisoquinoline**, m.p. 73°; **1-benzyl-3,4-dihydroisoquinoline**, b.p. 196° (12 mm.). **7,8-Dihydro-1,3-dioxolo[*g*]isoquinoline**, *6,7-methylenedioxy-3,4-dihydroisoquinoline*, $(CH_2O_2)C_6H_2(C_3H_5N)$, m.p. 91°, from formylhomopiperonylamide with P_2O_5; with HI it yields *hydrastinine hydriodide* (p. 369) (Ger. Pat. 234850, 1910). For the synthesis of hydrastinine and of cotarnine, which contains one more hydroxyl group, see the section on opium alkaloids (p. 369). **1,2-Dimethyl-1,2-dihydroisoquinoline**, b.p. 150° (20 mm.), and **2-methyl-1-benzyl-1,2-dihydroisoquinoline**, b.p. 170–180° (9 mm.), from 2-methylisoquinolinium iodide with CH_3MgI and $C_6H_5CH_2MgCl$, respectively.

Isocarbostyrils are *oxodihydroisoquinolines* (p. 253).

(*2*) **1,2,3,4-Tetrahydroisoquinolines** are prepared either synthetically by condensation of phenethylamines with aldehydes (p. 250 and *Pictet, Spengler*, Ber. **44**, 2030) or by reduction of isoquinolines and dihydroisoquinolines with Sn and hydrochloric acid, with Na and alcohol or catalytically with Ni and H_2 (Ger. Pat. 423026, 1923, Frdl. **XV**, 1454). An unusual synthesis is that from phenethylglycine chloride with $AlCl_3$, accompanied by loss of CO (*v. Braun, Wirz*, Ber. **60**, 102; Ger. Pat. 423027, 1924, Frdl. **XV**, 1711):

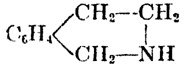


The tetrahydroisoquinolines behave like alkylated benzylamines, while tetrahydroquinoline has the properties of an alkylated aniline:



$$C_6H_4\left\langle\begin{array}{l}CH_2\text{—}CH_2\\ \quad\quad\quad\;\;|\\ NH\text{—}CH_2\end{array}\right.$$

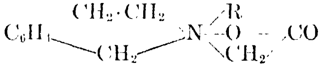
Tetrahydroquinoline



$$C_6H_4\left\langle\begin{array}{l}CH_2\text{—}CH_2\\ \quad\quad\quad\;\;|\\ CH_2\text{—}NH\end{array}\right.$$

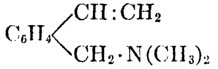
Tetrahydroisoquinoline

1,2,3,4-Tetrahydroisoquinoline, b.p. 233°, from phenethylamine, and concentrated hydrochloric acid, or by reduction of isoquinoline, is a strong base which absorbs CO_2 from the air; when warmed it reduces ammoniacal silver solution. Like piperidine (p. 220) it is oxidized by H_2O_2 to an N-oxide, m.p. 77°. Nitroso derivative, m.p. 33°; picrate m.p. 195°. **2,2-Dimethyltetrahydroisoquinolinium iodide**, $C_9H_{10}N(CH_3)_2I$, m.p. 189°, is formed from methyl iodide and tetrahydroisoquinoline. The **2-methyltetrahydroisoquinoline**, b.p. 212°, is best prepared by reduction of the 2-methylisoquinolinium iodide with Cu and hydrochloric acid; it is oxidized by chromic acid to N-methylphthalonimide (*Freund*, *Beck*, Ber. **37**, 1943). For the *Hofmann* decomposition of the dimethyl-1,2,3,4-tetrahydroisoquinolinium iodide to *o*-(N,N-dimethylaminomethyl)-styrene (I), see *v. Braun*, *Köhler*, Ber. **51**, 102. In contrast to the stability of the quinoline ring, the ring-fission in the isoquinoline series is not difficult; the isoquinoline ring opens very readily on exhaustive methylation (*cf.* the relative ring-stability of cyclic bases: *v. Braun*, Ber. **49**, 2629). **N-Ethyl-** and **N-propyltetrahydroisoquinoline** each yield with the 1-menthyl ester of iodoacetic acid two stereoisomeric addition products, $C_9H_{10}N(R)(CH_2COOC_{10}H_{19})I$, having different optical rotation; from these, by elimination of menthol with moist silver oxide, two pairs of betaines of the formula:



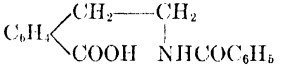
$$C_6H_4\begin{matrix}CH_2\cdot CH_2\\ \\ CH_2\end{matrix}N\begin{matrix}R\\ -O-\\ CH_2\end{matrix}CO$$

of opposite optical activity are formed. This is a synthesis of an optically active compound of pentavalent nitrogen (*Wedekind*, *Bandau*, Ann. **401**, 336; **404**, 322). **N-Benzoyltetrahydroisoquinoline**, b.p. 245-250° (50 mm.), is converted by oxidation with $KMnO_4$ to *β*-benzoylaminoethyl-*o*-benzoic acid [see formula (II) shown above]. The latter dehydrates readily to the benzoyl derivative of **hydroisocarbostyril** (III), m.p. 71° (*Bamberger*, *Dieckmann*, Ber. **26**, 1220).



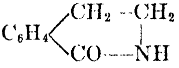
$$C_6H_4\left<\begin{matrix}CH:CH_2\\ CH_2\cdot N(CH_3)_2\end{matrix}\right.$$

(I)



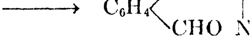
$$C_6H_4\left<\begin{matrix}CH_2—CH_2\\ COOH\quad NHCOC_6H_5\end{matrix}\right.$$

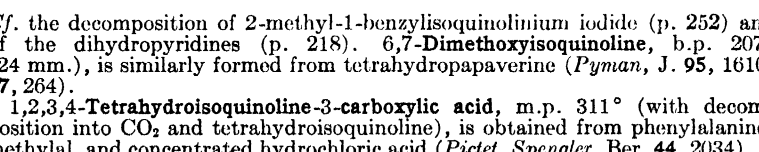
(II)



$$C_6H_4\left<\begin{matrix}CH_2—CH_2\\ CO—NH\end{matrix}\right.$$

(III)

1,2-Dimethyl-1,2,3,4-tetrahydroisoquinoline, b.p. 126° (20 mm.). **2-Methyl-1-benzyltetrahydroisoquinoline**, $C_9H_9(CH_2C_6H_5)NCH_3$, b.p. 178° (12 mm.), is the parent compound of *laudanosine* (p. 366); it is converted by the *Hofmann* reaction (p. 221) to *o*-vinylstilbene,  $C_6H_4\left<\begin{matrix}CH:CHC_6H_5\\ CH:CH_2\end{matrix}\right.$, (*Freund*, *Bode*, Ber. **42**, 1750). Oxidation with MnO_2 and dilute H_2SO_4 splits off the benzyl group in the form of benzaldehyde, leaving *o*-*β*-methylaminoethylbenzaldehyde, from which 2-methyldihydroisoquinolinium salts can be formed with acids (*Pyman*, J. **95**, 1738):



$$C_6H_4\left<\begin{matrix}CH_2——CH_2\\ CH(CH_2C_6H_5)\cdot N\cdot CH_3\end{matrix}\right. \longrightarrow C_6H_4\left<\begin{matrix}CH_2—CH_2\\ CHO\quad NHCH_3\end{matrix}\right. \underset{NaOH}{\overset{HI}{\rightleftarrows}} C_6H_4\left<\begin{matrix}CH_2—CH_2\\ CH{=}N(CH_3)I\end{matrix}\right.$$

Cf. the decomposition of 2-methyl-1-benzylisoquinolinium iodide (p. 252) and of the dihydropyridines (p. 218). **6,7-Dimethoxyisoquinoline**, b.p. 207° (24 mm.), is similarly formed from tetrahydropapaverine (*Pyman*, J. **95**, 1610; **97**, 264).

1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid, m.p. 311° (with decomposition into CO_2 and tetrahydroisoquinoline), is obtained from phenylalanine, methylal, and concentrated hydrochloric acid (*Pictet*, *Spengler*, Ber. **44**, 2034).

The homophthalimides are dioxotetrahydroisoquinolines, 1,3(2,4)-isoquinolinediones, while the phthalonimides are trioxo derivatives.

Other derivatives of tetrahydroisoquinoline are *berberine, hydrastine, narcotine, laudanosine,* and *apomorphine.*

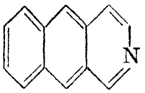
Decahydroisoquinoline has been obtained in two stereoisomeric modifications. The *cis-decahydroisoquinoline* is produced by catalytic reduction of isoquinoline with colloidal platinum (*Skita,* Ber. **57,** 1982) and by ring-closure of *cis*-hexahydro-*o*-homoxylylenediamine (*Helfer,* Helv. **6,** 785). The *trans*-compound is prepared by reduction of *trans*-hexahydrohomophthalimide with Na and amyl alcohol (*Helfer,* Helv. **9,** 814).

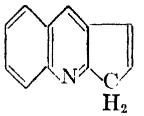
cis-Form: b.p. 97–98° (15 mm.); hydrochloride, m.p. 176°; chloroplatinate, m.p. 201°; picrate, m.p. 144°.

trans-Form: b.p. 81–83° (12 mm.); hydrochloride, m.p. 216°; chloroplatinate, m.p. 189°; picrate, m.p. 160°.

Benz[*g*]isoquinoline, 6,7-*benzisoquinoline, anthraisopyridine* (I), m.p. 166°, by reduction of the corresponding quinone, which is the condensation product of 4-benzoylnicotinic acid with concentrated H_2SO_4 (*Philips,* Ber. **28,** 1658).

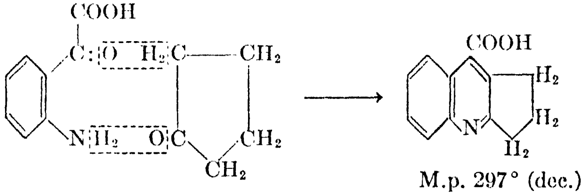
(I)





(II)

3-Cyclopenta[*b*]quinoline, quinindene (II). Partially hydrogenated derivatives of this ring system are obtained by condensation of isatin or isatic acid with cyclopentanones under the influence of aqueous KOH:

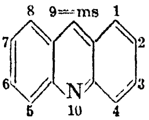


M.p. 297° (dec.)

1,2-Dihydro-3-cyclopenta[*b*]quinoline, 2,3-*trimethylenequinoline,* m.p. 60°, by decarboxylation of the carboxylic acid. The *hexahydro-3-cyclopenta[b]quinoline,* containing four more hydrogen atoms, exists in two stereoisomeric forms (*Perkin, Plant,* J. **1928,** 639).

(d) Acridines

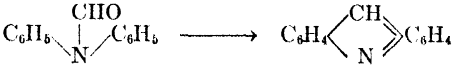
The acridine formula is derived from that of anthracene by replacement of one of the middle CH-groups with an N-atom. It may be designated 2,3,4,5- *or* lin.-dibenzopyridine:



For the distribution of the double bonds, see *v. Auwers, Kraul,* Ber. **58,** 543.

Its relation to quinoline and pyridine is evident from its oxidation to quinolinedicarboxylic acid and pyridinetetracarboxylic acid (pp. 242, 216). Acridines are prepared:

(*1*) From diphenylamine with carboxylic acids or from acyldiphenylamines by heating with $ZnCl_2$ (*Bernthsen,* Ann. **224,** 1):

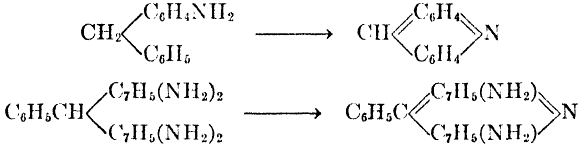


$$C_6H_5{\diagdown}\overset{CHO}{\underset{N}{|}}{\diagup}C_6H_5 \longrightarrow C_6H_4{<}^{CH}_{N}{>}C_6H_4$$

N-Formyldiphenylamine Acridine

From diphenylamine and homologous fatty acids, aromatic acids and dicarboxylic acids, *meso-* or 9-derivatives are obtained (*Hess*, *Bernthsen*, Ber. **18**, 690; *Jensen*, *Howland*, Am. **48**, 1988). Substituted diphenylamines, (*Besthorn*, *Curtman*, Ber. **24**, 2039), ditolylamine, phenylnaphthylamine, and similar compounds react like diphenylamine.

(*2*) Several acridine derivatives have been prepared from *o*-diamino derivatives of di- and triphenylmethane (*Fischer*, *Schülte*, Ber. **26**, 3085):

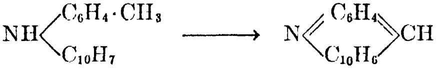


$$CH_2{<}^{C_6H_4NH_2}_{C_6H_5} \longrightarrow CH{<}^{C_6H_4}_{C_6H_4}{>}N$$

$$C_6H_5CH{<}^{C_7H_5(NH_2)_2}_{C_7H_5(NH_2)_2} \longrightarrow C_6H_5C{<}^{C_7H_5(NH_2)}_{C_7H_5(NH_2)}{>}N$$

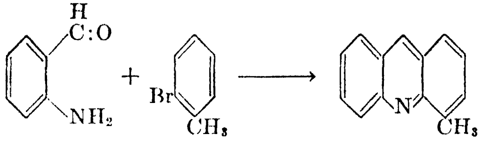
Benzacridines (naphthacridines) are formed by condensation of aldehydes with anilines and naphthols and also from *o*-aminobenzyl alcohol or *o*-aminobenzyl chlorides with naphthols or naphthylamines (*Ullmann*, *Fetvadjian*, Ber. **36**, 1027; *Ullmann*, *Fitzenkam*, Ber. **38**, 3787; *Baezner*, *Gardiol*, Ber. **39**, 2623; *Senier*, *Compton*, J. **91**, 1927).

(*3*) Benzacridines are produced by oxidation of *o*-tolylnaphthylamines with sulfur or PbO [*Ullmann*, *La Torre*, Ber. **37**, 2923; *Ullmann*, *Bühler*, Z. Farb. Textilchemie **4** (1906), 521]:



$$NH{<}^{C_6H_4\cdot CH_3}_{C_{10}H_7} \longrightarrow N{<}^{C_6H_4}_{C_{10}H_6}{>}CH$$

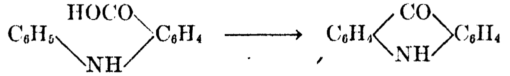
(*4*) Acridine derivatives can be synthesized by a variation of the *Friedländer* quinoline synthesis; thus, 4-methylacridine is prepared from *o*-aminobenzaldehyde and *o*-bromotoluene (*Jensen*, *Friedrich*, Am. **49**, 1049):



A similar reaction produces nitroacridines by the action of *o*-chlorobenzaldehyde on nitroanilines in the presence of copper powder (*Mayer*, *Stein*, Ber. **50**, 1306).

2,4-Dinitrobenzaldehyde condenses with benzene derivatives in the presence of concentrated H_2SO_4 to form acridones, with displacement of the negative substituents (*Tanasescu*, Bull. [4] **41**, 528).

(*5*) Acridones (p. 261) are formed by condensation of arylanthranilic acids, an adaptation of an anthraquinone synthesis (*Ullmann*, Ann. **355**, 318):

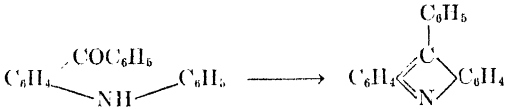


$$C_6H_5{\diagdown}\overset{HOCO}{\underset{NH}{\ }}{\diagup}C_6H_4 \longrightarrow C_6H_4{<}^{CO}_{NH}{>}C_6H_4$$

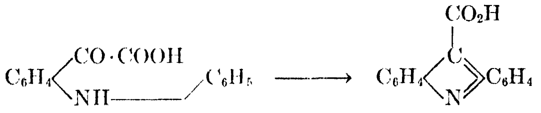
N-Phenylanthranilic acid Acridone

The condensation of phenols (naphthols, or the like) with N-acetylanthranilic acid gives similar products (*Schöpff*, Ber. **25**, 1983, 2740).

9-Phenylacridines result from the elimination of water from *o*-anilinobenzophenones by means of concentrated H_2SO_4 (*Ullmann*, *Ernst*, Ber. **39**, 298; *Ullmann*, *Broido*, Ber. **39**, 356):



Another example of this type of synthesis is the isomerization of N-arylisatins or the elimination of water from N-arylisatinic acid salts by heat, yielding salts of 9-acridinecarboxylic acids. By a similar reaction this acid is also prepared from diphenylamine, oxalyl chloride and $AlCl_3$ (*Friedländer, Kunz,* Ber. **55,** 1600; *Stollé,* J.pr. **105,** 137):



The acridines are very stable compounds. They are weaker bases than the pyridines and quinolines. They add alkyl iodides to form alkylacridinium iodides, which resemble the pyridinium, quinolinium, and isoquinolinium iodides (pp. 201, 230, 251), e.g., in their conversion to N-alkylacridones by alkaline potassium ferricyanide. When reduced, the acridines yield dihydroacridines, which are readily oxidized back to acridines. Acridine occurs in the crude anthracene from coal tar. Several of its derivatives are technically important as dyes. Because of their antiseptic action, a number of acridine compounds are used therapeutically; among these is trypaflavine or acriflavine [*Neuschaefer,* Med.Klin. **1918,** No. 34, 4 pp.; *Neufeld, Schiemann,* Deut.med.Woch. **45** (1919), 844; for a summary of its scope of applicability, see Pharm.Ber. (1927), 36]. Many acridine salts find use as seed disinfectants (Ger. Pat. 394255, 1919).

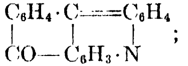
Acridine, m.p. 110°, sublimes even at 100°. Its solutions show a blue fluorescence. It is isomeric with phenanthridine and the benzoquinolines. In addition to the general syntheses given above, it is also prepared from diphenylamine and chloroform by heating with $ZnCl_2$ at 200° (*Fischer, Körner,* Ber. **17,** 101) and from acridone by distillation with zinc dust (*Rave, Tollens,* Ann. **276,** 58). Hydrochloride, yellow, m.p. 225°. With boiling sodium bisulfite solution acridine forms the sodium salt of 9,10-*dihydroacridine-9-sulfonic acid,* which can be used for the separation of acridine from a basic mixture (*Lehmstedt, Wirth,* Ber. **61,** 2044; Ger. Pat. 440771, 1925, Frdl. **XV,** 342). Acridine is oxidized by $KMnO_4$ to *acridinic acid,* 2,3-quinolinedicarboxylic acid. Metallic sodium converts it to a metallo-organic compound, which reacts with water to give 9,10-dihydroacridine (*Schlenk, Bergmann,* Ann. **463,** 281). When the acridinium compounds (see below) are oxidized, the heterocyclic ring is broken, and derivatives of diphenylamine-*o*-carboxylic acid, $C_6H_5 \cdot NH \cdot C_6H_4 \cdot COOH$, are formed.

Halogens react with acridine in chloroform or carbon disulfide solution to give loose addition compounds (perhalides) having the formula, $C_{13}H_9N(Hlg)_2$, which decompose into acridine in water, or even partially on standing. Perchloride, m.p. 240°; perbromide, m.p. 187°; periodide, m.p. 145° (*Senier, Austin,* J. **85,** 1196).

2-Methyl- and **4-methylacridine,** m.p. 134° and 88°, from *o*-aminobenzaldehyde and *p*- and *o*-bromotoluene (*Jensen, Friedrich,* Am. **49,** 1049).

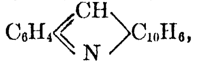
9-**Methylacridine**, m.p. 114°, from N-acetyldiphenylamine, like quinaldine and picoline, forms condensation products with benzaldehyde, with chloral and with formaldehyde (*Homberger, Jensen*, Am. **48**, 800): $C_{13}H_8NCH_2CH(OH)C_6H_5$, m.p. 197° (*Friedländer*, Ber. **38**, 2840), and $C_{13}H_8NCH_2CH(OH)CCl_3$. The latter product is transformed by alkali to 9-acridineacrylic acid, $C_{13}H_8NCH{:}CHCOOH$, which is oxidized by $KMnO_4$ to acridinecarboxaldehyde, $C_{13}H_8NCHO$, and then to 9-acridinecarboxylic acid, $C_{13}H_8NCOOH$ (*Bernthsen, Muhlert*, Ber. **20**, 1541). 9-**Benzylacridine**, $C_{13}H_8(CH_2C_6H_5)N$, m.p. 173°, from diphenylamine with phenylacetic acid and $ZnCl_2$ at 200° (*Decker, Hock*, Ber. **37**, 1565).

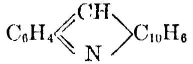
9-**Phenylacridine**, m.p. 181°, from diphenylamine and benzoic acid, crystallizes from benzene with benzene of crystallization. 9-*p*-**Dimethylaminophenylacridine**, $(C_{13}H_8)C_6H_4N(CH_3)_2$, m.p. 279°, by condensation of acridone and dimethylaniline with $POCl_3$ (*Ullmann, Bader, Labhardt*, Ber. **40**, 4795). 9-**Phenylacridol**, see *Landauer*, Bull. [3] **31**, 1083. 9-**Acridine-*o*-benzoic acid**, $N(C_6H_4)_2{:}CC_6H_4COOH$, m.p. 347°, is obtained from diphenylamine and phthalic acid; when warmed with methyl iodide it is converted into the hydriodide of its methyl ester, m.p. 173° (*Decker, Hock*, Ber. **37**, 1007). With fuming sulfuric acid it condenses to a compound combining an anthraquinone and an acridine nucleus:



$$\begin{array}{l} C_6H_4\cdot C{=\!=\!=}C_6H_4 \\ |\qquad\ |\qquad\ | \\ CO{-}C_6H_3\cdot N \end{array}$$

; this compound is also obtained from 1-anilinoanthraquinone, and resembles the ceroxenes (p. 192) in formation and behavior [*Dammann, Gattermann*, Z.Farb.Textilchemie **1** (1902), 325; *Decker*, Ann. **348**, 242].

Benz[*a*]acridine (*β-naphthacridine*),  $C_6H_4{<}\genfrac{}{}{0pt}{}{CH}{N}{>}C_{10}H_6$, m.p. 131°, from formaldehyde, aniline, and 2-naphthol, from *o*-aminobenzyl alcohol or *o*-aminobenzyl chloride with 2-naphthol (*Ullmann, Baezner*, Ber. **35**, 2670; *Baezner*, Ber. **37**, 3078) and from *o*-tolyl-2-naphthylamine by oxidation with PbO. An unusual formation of the benzacridine nucleus occurs when dihydronaphtho-[2,1-*b*]furan-1,2-dione is digested with two molar proportions of aniline in glacial acetic acid, which yields 9-benz[*a*]acridinecarboxylic acid, m.p. 284° (*Safteiu*, Ber. **58**, 1958). **Benz[*c*]acridine** (*α-naphthacridine*),



$$C_6H_4{<}\genfrac{}{}{0pt}{}{CH}{N}{>}C_{10}H_6$$

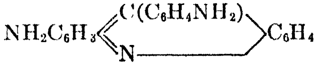
m.p. 108°, by oxidation of *o*-tolyl-1-naphthylamine with PbO (*Ullmann, La Torre*, Ber. **37**, 2922). Benz[*a*]- and benz[*c*]acridine are formed pyrogenically from N-benzylidene-1- and 2-naphthylamine, $C_6H_5CH{:}NC_{10}H_7$, although N-benzylideneaniline under the same conditions yields phenanthridine (p. 264), not acridine.

Of the six theoretically possible dibenzacridines, four are known (*Simon, Maugrin*, C.r. **143**, 427): **dibenz[*ah*]acridine**, m.p. 228°, and **dibenz[*aj*]acridine**, m.p. 216°, from trioxymethylene and 2-naphthol with 1- and 2-naphthylamine, respectively (*Ullmann, Fetvadjian*, Ber. **36**, 1027. **Dibenz[*ch*]acridine**, m.p. 185°, from dichloromethane and 1-naphthylamine. The fourth isomer, **dibenz[*ai*]acridine**, m.p. 203°, has been prepared by distillation of the corresponding dibenzacridone with zinc dust (*Strohback*, Ber. **34**, 4146; *cf. Möhlau, Haase*, Ber. **35**, 4164). **Tetrabenz[*a,c,h,j*]acridine**, *diphenanthracridine*, from dichloromethane and 9-aminophenanthrene (*Austin*, J. **93**, 1760).

NITROACRIDINES. 2-Nitroacridine, m.p. 215°, and 4-**nitroacridine**, m.p. 167°, by nitration of acridine (*Mayer, Stein*, Ber. **50**, 1306; *Lehmstedt*, Ber. **60**, 1370). The 4-nitro derivative is also obtained from *o*-chlorobenzaldehyde and *o*-nitroaniline in the presence of Cu-powder (*Mayer, Stein*, Ber. **50**, 1306).

AMINOACRIDINES. 4-**Aminoacridine**, m.p. 105°, by reduction of the corresponding nitro compound (*Lehmstedt*, Ber. **60**, 2413).

CHRYSANILINE, 9-*p*-**aminophenyl**-2-**aminoacridine**:



$$NH_2C_6H_3{<}\genfrac{}{}{0pt}{}{C(C_6H_4NH_2)}{N}{>}C_6H_4$$

m.p. 268°, is the principal constituent of the dye **phosphin**, which is formed as a side-product in the manufacture of rosaniline (Vol. III, p. 534). The salts are red, give solutions having a yellow-green fluorescence, and dye silk and wool a beautiful yellow. The formation of chrysaniline from pararosaniline follows the equation for method *2* for the preparation of acridines (p. 257).

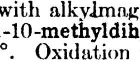
A series of amino derivatives of acridine, 9-phenylacridine and the corresponding alkylacridinium salts are yellow to orange-red dyes (*Ullmann, Marié*, Ber. **34**, 4307). These include 3,6-**diaminoacridine**, m.p. 284° (brown-yellow), first obtained from tetraaminodiphenylmethane by heating with tin salts in an autoclave, but produced in better yield from *m*-phenylenediamine by heating with formic acid in the presence of glycerol and dehydrating agents (Ger. Pat. 347819, 1920, Frdl. **XIV**, 799). **Acriflavine, trypaflavine,** 3,6-*diamino*-10-*methylacridinium chloride*, used as an antiseptic. **Rivanol**, 2-*ethoxy*-6,9-*diaminoacridine lactate* (Apoth.-Ztg. **44**, No. 58; C. **1929**, **II**, 2074). **Acridine yellow,** 2,7-*dimethyl*-3,6-*diaminoacridine*, prepared from tetraaminoditolylmethane by heating with hydrochloric acid and oxidizing with ferric chloride. **Benzoflavine,** 9-*phenyl*-3,6-*diamino*-2,7-*dimethylacridine*, m.p. 231°, from benzaldehyde and *m*-toluylenediamine (*Meyer, Gross*, Ber. **32**, 2352).

9-**Amino-** or **alkylaminoacridines**, which can be obtained from the reaction of 9-chloroacridines with ammonia and aliphatic amines, are of interest because of their quinine-like action (Ger. Pat. 360421, 1919, Frdl. **XIV**, 800; and numerous supplementary patents).

9-**Ethylaminoacridine,** m.p. 145°, from 9-acridinepropionic acid by the *Curtius* reaction.

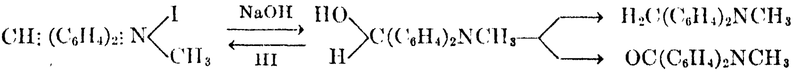
CARBOXYLIC ACIDS. 9-**Acridinecarboxylic acid,** m.p. 290° (*Lehmstedt, Wirth*, Ber. **61**, 2044). 9-**Acridinepropionic acid,** methyl ester, m.p. 95°, by heating diphenylamine with succinic acid and $ZnCl_2$ at 200° (*Jensen, Howland*, Am. **48**, 1988).

HYDROACRIDINES. 9,10-**Dihydroacridine,** *ms*-acridane, $NH(C_6H_4)_2CH_2$, m.p. 168°, results from reduction of acridine with zinc dust and hydrochloric acid or with sodium amalgam in alcoholic solution. The basic properties of acridine are lost in the conversion to dihydroacridine. The latter reduces ammoniacal silver nitrate with the regeneration of acridine. It has been found in coal tar (*Decker, Dunant*, Ber. **42**, 1178). 10-**Methyl-** and 10-**phenyldihydroacridine,** m.p. 96° and 119°, by reduction of the corresponding acridones (*Decker, Dunant*, Ber. **39**, 2720; *Ullmann, Maag*, Ber. **40**, 2515). A number of alkylated 9,10-dihydroacridines have been obtained by the reaction of 10-alkylacridinium iodides with alkylmagnesium halides: 9,10-**dimethyl-**, 9-**ethyl-**, 9-**benzyl-**, and 9-**phenyl**-10-**methyldihydroacridine,** $CH_3N(C_6H_4)_2CHR$, m.p. 138°, 72°, 108°, and 104°. Oxidation with iodine solution converts these dihydroacridines into the methyl iodide addition products of 9-alkylacridines, which can again be treated with alkylmagnesium halides (*Freund, Bode*, Ber. **42**, 1746). Derivatives of 9,9-dialkyl(or diaryl)-9,10-dihydroacridines have been prepared by the action of alkyl(or aryl)magnesium halides on N-phenylanthranilic acid methyl ester (*Goldstein, Kopp*, Helv. **11**, 478, 486).

1,2,3,4-**Tetrahydroacridines** have been synthesized by adaptation of methods 2 and 4*e* for the preparation of quinolines (pp. 226, 228) to ketones of the cyclohexane series: (*1*) by condensation of cyclohexanones with aromatic *o*-aminoaldehydes and ketones; (*2*) by condensation of 2-acylcyclohexanones with aniline and its homologues (*Borsche* Ann. **377**, 70; Ber. **41**, 2206). 1,2,3,4-**Tetrahydroacridine**  $C_6H_4{<}\genfrac{}{}{0pt}{}{CH}{N}{>}C_6H_8$, m.p. 55°, is converted to acridine by distillation over lead oxide; it is best obtained through its 9-carboxylic acid (*Perkin, Sedgwick*, J. **125**, 2437).

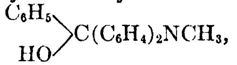
1,2,3,4,9,10,9a,9b-**Octahydroacridine**, two racemic forms, m.p. 82° and 72°, by further reduction of tetrahydroacridine (*Perkin, Sedgwick*, J. **125**, 2437; resolution of the rac. forms: *Perkin, Sedgwick*, J. **1926**, 438). *Perhydroacridine*, m.p. 80°, b.p. 140° (14 mm.); picrate, m.p. 167° (*v. Braun, Petzold, Schultheiss*, Ber. **56**, 1347). Hydrogenated acridine derivatives have been patented as insecticides (Ger. Pat. 409509, 1923).

ALKYLACRIDINIUM COMPOUNDS. 10-**Methylacridinium iodide,** $C_{13}H_9N$-(CH_3I), reacts like the alkyl iodide addition products of pyridine, quinoline, and isoquinoline (pp. 201, 230, and 251). With sodium hydroxide **10-methyl-9,10-dihydro-9-acridol** is formed, due to a rearrangement of the unstable base (*Bünzly, Decker*, Ber. **37**, 576). The methyldihydroacridol is converted by acids to acridinium salts, by alkaline potassium ferricyanide solution to 10-methylacridone, and by warming with aqueous sodium hydroxide alone to a mixture of 10-methyldihydroacridine and 10-methylacridone (*Pictet, Patry*, Ber. **35**, 2534):

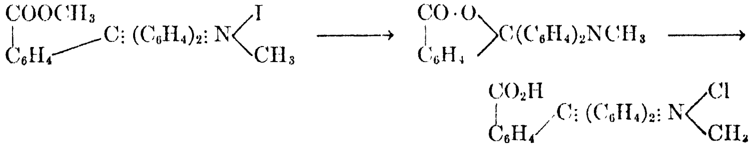


$$CH{:}(C_6H_4)_2{:}N\begin{smallmatrix}I\\CH_3\end{smallmatrix} \underset{HI}{\overset{NaOH}{\rightleftarrows}} \begin{smallmatrix}HO\\H\end{smallmatrix}{>}C(C_6H_4)_2NCH_3 \begin{smallmatrix}\rightarrow H_2C(C_6H_4)_2NCH_3\\ \rightarrow OC(C_6H_4)_2NCH_3\end{smallmatrix}$$

By an analogous reaction, **9-phenyl-10-methylacridinium iodide** yields 9-phenyl-10-methyl-9-dihydroacridol,

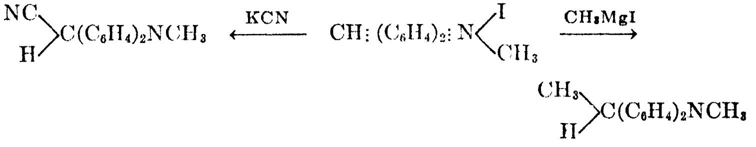


$\begin{smallmatrix}C_6H_5\\HO\end{smallmatrix}{>}C(C_6H_4)_2NCH_3$, which is also obtained from 10-methylacridone with phenylmagnesium bromide, and which regenerates the acridinium salts when treated with acids (*Bünzly, Decker*, Ber. **37**, 575). Instead of the hydracridol, 10-methyl-9-benzylacridinium iodide gives **10-methyl-9-benzylidenedihydroacridine**, $C_6H_5CH{:}C(C_6H_4)_2NCH_3$, m.p. 141 °, which decomposes readily into benzaldehyde and 10-methylacridone (*Decker, Hock*, Ber. **37**, 1564). By an analogous reaction, the methyl iodide addition product of 9-acridinebenzoic acid ester is converted by aqueous sodium hydroxide into 10-methyldihydro-9-hydroxyacridinebenzoic acid lactone, m.p. 245 °, which yields the methyl chloride addition product of acridinebenzoic acid when treated with hydrochloric acid (*Decker, Hock*, Ber. **37**, 1002):



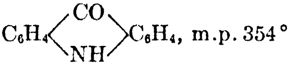
$$\begin{smallmatrix}COOCH_3\\|\\C_6H_4\end{smallmatrix}\!-\!C{:}(C_6H_4)_2{:}N\begin{smallmatrix}I\\CH_3\end{smallmatrix} \longrightarrow \begin{smallmatrix}CO\cdot O\\|\\C_6H_4\end{smallmatrix}{>}C(C_6H_4)_2NCH_3 \longrightarrow \begin{smallmatrix}CO_2H\\|\\C_6H_4\end{smallmatrix}\!-\!C{:}(C_6H_4)_2{:}N\begin{smallmatrix}Cl\\CH_3\end{smallmatrix}$$

With alkylmagnesium halides the alkylacridinium iodides give 9,10-dihydroacridines (see above), and with potassium cyanide, 10-alkyl-9-cyanodihydroacridines (*Freund, Bode*, Ber. **42**, 1746; *Kaufmann, Albertini*, Ber. **44**, 2052):

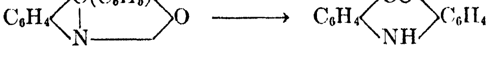


$$\begin{smallmatrix}NC\\H\end{smallmatrix}{>}C(C_6H_4)_2NCH_3 \xleftarrow{KCN} CH{:}(C_6H_4)_2{:}N\begin{smallmatrix}I\\CH_3\end{smallmatrix} \xrightarrow{CH_3MgI} \begin{smallmatrix}CH_3\\H\end{smallmatrix}{>}C(C_6H_4)_2NCH_3$$

9(10)-**ACRIDONE**, **9-oxo-9,10-dihydroacridine**,



$C_6H_4\begin{smallmatrix}CO\\NH\end{smallmatrix}C_6H_4$, m.p. 354 °, is prepared from acridine by the action of calcium oxychloride in the presence of cobalt salts. It is synthesized from phenylanthranilic acid with H_2SO_4 at 100 ° and from salicylanilide by dry distillation, presumably after a preliminary rearrangement into phenylanthranilic acid; salicyltoluides yield methylated acridones (*Pictet, Hubert*, Ber. **29**, 1189). An interesting formation of acridone is the rearrangement of C-phenylanthranil when heated alone or by the simultaneous action of concentrated H_2SO_4 and nitrous acid (*Kliegl*, Ber. **42**, 592; *Bamberger*, Ber. **42**, 1716):

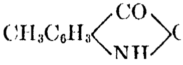
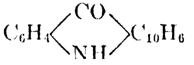
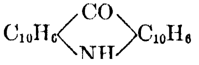


$$C_6H_4\begin{smallmatrix}C(C_6H_5)\\|\\N\end{smallmatrix}O \longrightarrow C_6H_4\begin{smallmatrix}CO\\NH\end{smallmatrix}C_6H_4$$

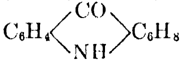
(*cf.* the conversion of C-methylanthranil into indoxyl). With methyl iodide and alkali, acridone gives **10-methylacridone**, $CO(C_6H_4)_2NCH_3$, m.p. 203 °, whose formation from methylacridinium iodide is mentioned above. With phosphorus sulfide the product is **thioacridone**, *9-thio-9,10-dihydroacridine*, $CS(C_6H_4)_2NH$

or $HS{\cdot}C(C_6H_4)_2N$, m.p. 275°, which is also obtained from acridine by heating with sulfur. Thioacridone is acidic, and is alkylated on the sulfur atom by alkali and alkyl halides: **9-methylmercaptoacridine**, $N(C_6H_4)_2CSCH_3$, m.p. 114°. With PCl_5, both acridone and thioacridone give **9-chloroacridine**, m.p. 119°. **9-Bromoacridine**, m.p. 116°, from thioacridone with phosphorus bromide. **9-Iodoacridine**, m.p. 169°, from bromoacridine with NaI (*Edinger, Arnold*, J.pr. **64**, 471). When 10-methylacridone is heated with PCl_5, 10-methylchloroacridinium chloride, m.p. 73°, is formed; this reacts with aniline to give 10-methyl-9-anilinoacridinium chloride, the hydroxide of which can be converted by elimination of water to the **anil of 10-methylacridone**, $C_6H_5N{:}C(C_6H_4)_2NCH_3$, m.p. 163° (*Fischer, Demeler*, Ber. **32**, 1309). Acridone is reduced by zinc dust to acridine, and by Na and alcohol to dihydroacridine. For the reduction of 10-methylacridone, see *Decker, Dunant*, Ber. **42**, 1176. **10-Phenylacridone**, $CO(C_6H_4)_2N{-}C_6H_5$, m.p. 276°, from diphenylanthranilic acid and concentrated H_2SO_4 (*Goldberg, Nimerovsky*, Ber. **40**, 2450).

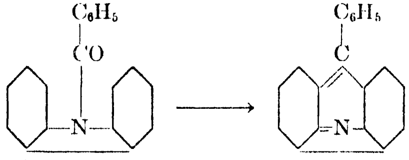
The following derivatives are obtained by methods similar to those used for acridone itself: **4-methylacridone** (I), m.p. 346°; **2-methylacridone**, m.p. 338°; **2,4-dimethylacridone**, m.p. 297° (*Kaufmann*, Ann. **279**, 281; *Ullmann*, Ann. **355**, 318); **benzacridone** (II), **dibenzacridone** (III) (see *Schopff*, Ber. **25**, 2744).

(I)  $CH_3C_6H_3\Big<\begin{matrix}CO\\NH\end{matrix}\Big>C_6H_4$ (II)  $C_6H_4\Big<\begin{matrix}CO\\NH\end{matrix}\Big>C_{10}H_6$ (III)  $C_{10}H_6\Big<\begin{matrix}CO\\NH\end{matrix}\Big>C_{10}H_6$

For **naphthacridinetrione**, see *Ullmann, Sone*, Ann. **380**, 336; Ger. Pats. 221853 and 237236 (1910) and 246966 (1911), Frdl. **X**, 703, 708, 725.

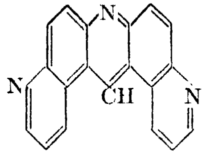
1,2,3,4-Tetrahydroacridone,  $C_6H_4\Big<\begin{matrix}CO\\NH\end{matrix}\Big>C_6H_8$, m.p. 238°, by condensation of cyclohexanone with anthranilic acid (*Tiedtke*, Ber. **42**, 621; *Perkin, Sedgwick*, J. **125**, 2437). **Decahydroacridine-1,8-dione**, $CH_2(C_6H_6O)_2NH$, from 2,2′,6,6′-tetrahydroxydiphenylmethane with alcoholic NH_3, is reduced with zinc dust to acridine, and is oxidized by N_2O_3 to octahydroacridinedione, m.p. 141° (*Vorländer* Ann. **309**, 353).

Peculiar acridine derivatives are formed by the condensation of acylcarbazoles (*Bizzarri*, Gazz. **21**, II, 158, 351):

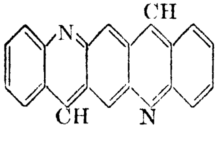


N-Benzoylcarbazole 9-Phenylcarbazacridine, m.p. 186°

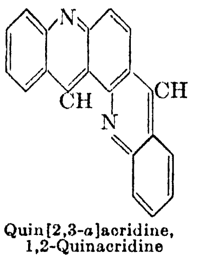
The compounds containing an acridine nucleus joined to one or two pyridine nuclei or a quinoline nucleus are known as **pyracridines** or **quinacridines**:



Dipyrid[3,2-*a*, 2′,3′-*j*]acridine,
Dipyracridine



Quin[2,3-*b*]acridine,
2,3-Quinacridine

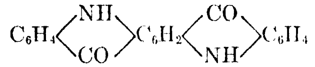


Quin[2,3-*a*]acridine,
1,2-Quinacridine

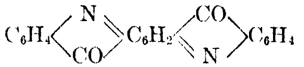
Dipyrid[3,2-*a*, 2′,3′-*j*]acridine, *dipyracridine*, m.p. 303°, is formed by the condensation of dichloromethane with 6-aminoquinoline; **benzo[*a*]pyrid[2,3-*j*]-**

acridine and **benzo[*h*]pyrid[3,2-*a*]acridine** (the *naphthopyridacridines*), m.p. 220° and 268°, are prepared from dichloromethane with 6-aminoquinoline and 2- and 1-naphthol (*cf.* method *2* for the synthesis of acridines, p. 257) (*Senier, Compton*, J. **95**, 1623).

Quin[2,3-*b*]acridine, yellow needles, m.p. 245°, is obtained from the product of the condensation of *p*-phenylenedianthranilic acid with concentrated H_2SO_4, quinacridone (I), yellow needles, m.p. 394°, by reduction with sodium and alcohol to the **dihydroquinacridine**, red needles, m.p. 243°, and subsequent oxidation with $FeCl_3$ or HNO_3. The quinacridone is converted by oxidation with PbO_2 in benzene in the presence of glacial acetic acid to a compound containing two less hydrogen atoms, the quinone-like **dehydroquinacridone** (II), which

(I) 

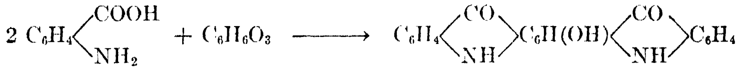
$$C_6H_4\left\langle\begin{matrix}NH\\CO\end{matrix}\right\rangle C_6H_2\left\langle\begin{matrix}CO\\NH\end{matrix}\right\rangle C_6H_4$$

 (II)

$$C_6H_4\left\langle\begin{matrix}N\\CO\end{matrix}\right\rangle C_6H_2\left\langle\begin{matrix}CO\\N\end{matrix}\right\rangle C_6H_4$$

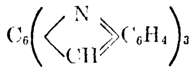
forms blue-black flakes giving a blue solution with benzene and which has strong oxidizing properties (*Ullmann, Maag*, Ber. **39**, 1693; **40**, 2522; *Kalb*, Ber. **43**, 2209).

The isomeric **quin[2,3-*a*]acridine**, m.p. 213°, is prepared by zinc dust distillation of the hydroxyquinacridone formed when phloroglucinol and anthranilic acid are heated together:



$$2\ C_6H_4\left\langle\begin{matrix}COOH\\NH_2\end{matrix}\right. + C_6H_6O_3 \longrightarrow C_6H_4\left\langle\begin{matrix}CO\\NH\end{matrix}\right\rangle C_6H(OH)\left\langle\begin{matrix}CO\\NH\end{matrix}\right\rangle C_6H_4$$

Phloroglucinol condenses similarly with *o*-aminobenzaldehyde to quinacridinol, garnet-black needles, m.p. 360°; at the same time 1 mol of the first reactant condenses with 3 mols of the second to give **phloroquinyl**, *diquin*[2,3-*a*, 2′,3′-*c*] *acridine:*

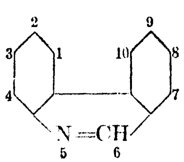


$$C_6\left(\left\langle\begin{matrix}N\\CH\end{matrix}\right\rangle C_6H_4\right)_3$$

yellow-brown needles, m.p. 403°, a ring homologue of pyrido[2,3-*f*][1,7]phenanthroline (p. 265) (*v. Niementowski*, Ber. **29**, 76; **39**, 385). For **biacridines**, see *Bäzner*, Ber. **39**, 2650.

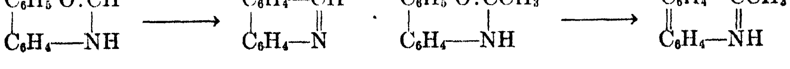
(e) Phenanthridine

Phenanthridine may be regarded as a benzo derivative of quinoline, and also of isoquinoline. Its name is derived from phenanthrene and pyridine, since its formula is the phenanthrene formula with a nitrogen atom in place of one of the middle methine groups:



Phenanthridine is isomeric with the benzoquinolines (p. 247).

Phenanthridines are prepared by heating the acyl derivatives of *o*-aminodiphenyl (*Pictet, Hubert*, Ber. **29**, 1182):



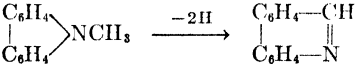
$$\begin{matrix}C_6H_5\ O{:}CH\\ |\qquad\ \ |\\ C_6H_4\text{—}NH\end{matrix} \longrightarrow \begin{matrix}C_6H_4\text{—}CH\\ |\qquad \|\\ C_6H_4\text{—}N\end{matrix} \cdot \begin{matrix}C_6H_5\ O{:}CCH_3\\ |\qquad\ \ |\\ C_6H_4\text{—}NH\end{matrix} \longrightarrow \begin{matrix}C_6H_4\text{—}CCH_3\\ \|\qquad \|\\ C_6H_4\text{—}NH\end{matrix}$$

Phenanthridine, m.p. 104°, b.p. over 360°, is also obtained by pyrolysis of N-benzylideneaniline (optimum temperature: 800°, porcelain tube: *Pyl,* Ber. **60,** 287):

$$C_6H_5CH{=}NHC_6H_5 \xrightarrow{-2H} C_6H_4CH{=}NC_6H_4$$

The corresponding N-benzylidenenaphthylamines give derivatives of acridine (see p. 259). Also, benzylaniline, containing two more atoms of hydrogen, gives acridine when decomposed with a glowing platinum wire (*Meyer, Hofmann,* Ber. **37,** 681).

Phenanthridine is formed from N-methylcarbazole in the same way that pyridine is obtained from N-methylpyrrole (p. 201), and quinoline from 2-methylindole (p. 229, and *Pictet,* Ber. **38,** 1950):

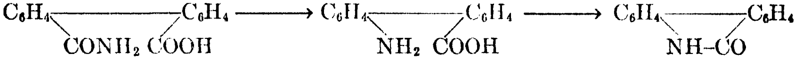


It is also prepared by the distillation of phenanthridone with zinc dust. Oxidation with calcium oxychloride and cobalt nitrate converts it to phenanthridone (*Pictet, Patry,* Ber. **26,** 1964) and reduction with tin and hydrochloric acid, to **dihydrophenanthridine,** m.p. 90° (*Pictet, Ankersmit,* Ann. **266,** 142):

$$C_6H_4CH_2{-}NHC_6H_4$$

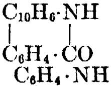
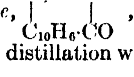
6-Methyl-, 6-**ethyl-,** and 6-**phenylphenanthridine,** m.p. 85°, 55°, and 109° (*Pictet, Hubert,* Ber. 29, 1184).

6(5)-**Phenanthridone,** $C_6H_4CO{-}NHC_6H_4$, m.p. 293°, is obtained from phenanthrene *via* diphenamic acid by treatment with bromine and alkali (*Oyster, Adkins,* Am. **43,** 208):



Phenanthridones substituted in the benzene nucleus have been synthesized by this method (*Moore, Huntress,* Am. **49,** 1324). Phenanthridone also results from the rearrangement of 1-aminofluorenone on fusion with alkali and of fluorenone oxime by means of zinc chloride or PCl_5 (*Moore, Huntress,* Am. **49,** 2618), and finally from *o*-diphenylylurethan, $C_6H_5C_6H_4NHCO_2C_2H_5$, by heating with zinc chloride (*Graebe, Lagodzinski,* Ann. **276,** 35; *Graebe, Schestakow,* Ann. **284,** 306; *Kerp,* Ber. **29,** 230; *Pictet, Hubert,* Ber. **29,** 1188). It can be prepared from phenanthridine by boiling with calcium oxychloride in the presence of cobalt salts (*Meyer, Hofmann,* Mo. **37,** 701). With PCl_5 phenanthridone gives 6-**chlorophenanthridine,** $C_6H_4CCl{=}NC_6H_4$, m.p. 116°. **5-Methyl-6(5)-phenanthridone,** m.p. 108°, is also formed from 5-methylphenanthridinium iodide, $C_{13}H_9N \cdot ICH_3$, with aqueous sodium hydroxide, together with the steam-volatile 5-methyldihydrophenanthridine, $C_{13}H_{20}NCH_3$ (*Pictet, Patry,* Ber. **35,** 2534) (*cf.* the analogous reaction with the pyridinium, quinolinium, and isoquinolinium compounds, pp. 201, 230, 251).

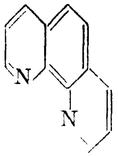
3-**Nitro-6(5)-phenanthridone,** m.p. 349°; 8-**nitro-6(5)-phenanthridone,** m.p. 293° (*Hozer, v. Niementowski,* J.pr. **116,** 43).

Benzo[*c*]phenanthridone, *α-naphthophenanthridone,*  $\begin{array}{l} C_{10}H_6{\cdot}NH \\ | \qquad | \\ C_6H_4{\cdot}CO \end{array}$, m.p. 332°, and **benzo[*i*]phenanthridone,** *β-naphthophenanthridone,*  $\begin{array}{l} C_6H_4{\cdot}NH \\ | \qquad | \\ C_{10}H_6{\cdot}CO \end{array}$, m.p. 338°, from *α*- and *β*-chrysodiphenamic acid, are converted by distillation with zinc dust into **benzo[c]phenanthridine**, m.p. 135°, and **benzo[i]phenanthridine**, m.p. 182° (*Graebe*, Ann. **335**, 124).

The ring systems treated in the last four sections contain a pyridine ring combined with one or more benzene rings. The reverse situation, in which a benzene ring is flanked by several pyridine rings, occurs in a number of ring systems. (There are 28 possible isomers.) Here also there is a tendency toward angular union of the third ring.

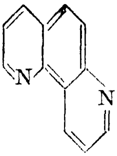
The most important of these systems are the phenanthrolines (I, II, III):

(I)



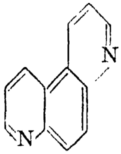
1,10-Phenanthroline,
o-Phenanthroline

(II)



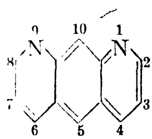
1,7-Phenanthroline,
m-Phenanthroline

(III)

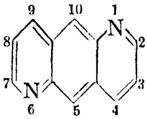


4,7-Phenanthroline,
p-Phenanthroline

They are prepared by a double *Skraup* synthesis from *o*-, *m*-, and *p*-phenylenediamine or by the formation of one pyridine ring, starting from 8-amino- (for I), 7-amino- (for II) and 6-aminoquinoline (for III). While with *o*-phenylenediamine the reaction can only produce I, with *m*- and *p*-phenylenediamine, a linear arrangement is also possible for the two pyridine rings; this would lead to ring systems of the following type, for which members are not yet known:



1,9-Derivative,
Pyrido[3,2-*g*]quinoline*



1,6-Derivative,
Pyrido[2,3-*g*]quinoline*

That the angular ring systems are formed exclusively is evident from the products of their oxidation, dicarboxylic acids which are converted by decarboxylation to derivatives of 2,2′-, 2,3′-, and 3,3′-bipyridines (*Smith*, Am. 52, 397).

1,10(or *o*)-**Phenanthroline**, hydrate m.p. 102°, anhydrous m.p. 117°, b.p. 360°, from *o*-phenylenediamine by the *Skraup* synthesis; with silver salts, on oxidation with ammonium persulfate, it forms a very stable complex salt of divalent silver (*Hieber*, *Mühlbauer*, Ber. **61**, 2149). 1,7(or *m*)-**Phenanthroline**, $C_{12}H_8N_2(+ 2H_2O)$, m.p. (65°) 78°, from *m*-diaminobenzene (*Smith*, Am. **52**, 397) or 7-aminoquinoline (*Skraup*, *Vortmann*, Mo. **4**, 569; *Marckwald*, Ber. **23**, 1016). 4,7(or *p*)-**Phenanthroline**, *pseudophenanthroline*, m.p. 173°, from 3-aminoquinoline, *p*-diaminobenzene (*Smith*, Am. **53**, 397) or aminoazobenzene with glycerol and sulfuric acid, is oxidized by $KMnO_4$ to 2,3- and 3,3-bipyridinedicarboxylic acids (p. 206) (*Kaufmann*, *Radošević*, Ber. **42**, 2612). For phenyl-1,7- and phenyl-4,7-phenanthrolinecarboxylic acid, from 7- and 6-aminoquinoline with benzaldehyde and pyruvic acid, see *Willgerodt*, *Jablonski*, Ber. **33**, 2918; *Willgerodt*, *v. Neander*, Ber. **33**, 2928.

In conclusion, **pyrido[2,3-*f*][1,7]phenanthroline**, *phenotripyridine*, $C_6(C_3H_3N)_3$, m.p. 236°, should be mentioned. This compound, which contains three pyridine nuclei joined to a benzene nucleus, is prepared from 1,3,5-triaminobenzene by the *Skraup* synthesis; it is very resistant to oxidizing agents (*Pictet*, *Barbier*, Bull. [3] **13**, 28).

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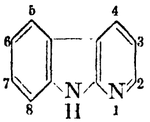
* These two compounds have since been reported: *Ruggli*, *Staub*, Helv. **20**, 919; *Ruggli*, *Preiswerk*, Helv. **22**, 484.

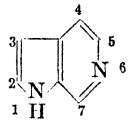
4. SYSTEMS CONTAINING TWO OR MORE ADJACENT CONDENSED HETEROCYCLIC RINGS

(a) Heterocyclic Rings Having C—C in Common

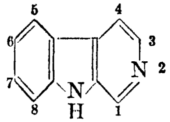
1. The **carboline bases,** *harmyrine* and *norharman,* contain a combination of a pyridine and a pyrrole or indole ring:



9-Pyrid[2,3-*b*]indole, Carboline, m.p. 210°



1-Pyrrolo[2,3-*c*]-pyridine, Harmyrine

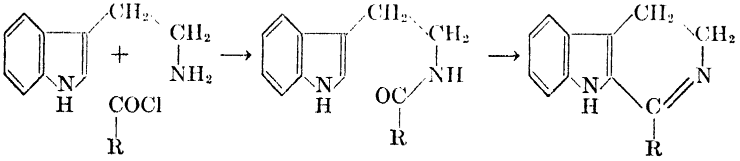


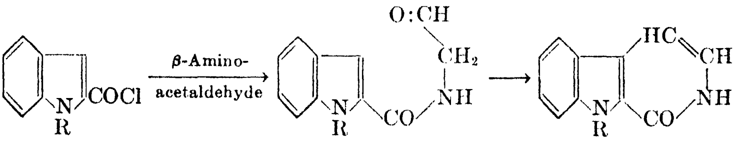
9-Pyrid[3,4-*b*]-indole, Norharman

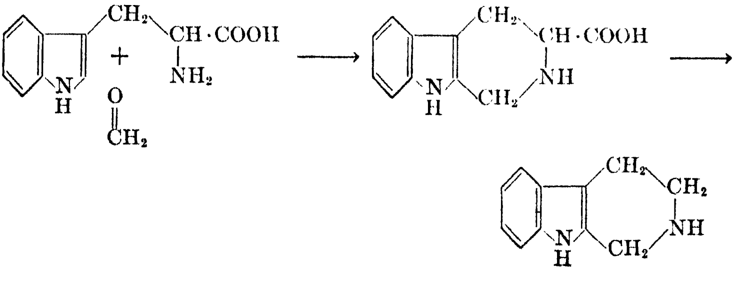
Carbolinium compounds have been prepared from 2-chloropyridine and *o*-phenylenediamine over various intermediate products (*Lawson, Perkin, Robinson,* J. **125**, 626).

The most important of these compounds is **norharman,** since it is the parent compound of a series of alkaloids in the rue of the Turkestan steppes (*Peganum harmala*), including **harmeline** and **harmine** (see the section on alkaloids).

For the synthesis of the norharman structure, several methods have been developed: (*1*) Starting from 3-(*β-aminoethyl*)*indole,* by joining the pyridine ring according to the isoquinoline syntheses (*Späth, Lederer,* Ber. **63**, 120, 2102). (*2*) Starting from N-substituted indole-2-carboxylic acids, which are reacted in the form of their acid chlorides with β-aminoacetaldehyde or its dimethyl acetal, to form an intermediate product which is converted into 1-oxo-1,2-dihydronorharman by warming with alcoholic HCl (*Kermack, Perkin, Robinson,* J. **119**, 1602; **121**, 1872). (*3*) From *tryptophan,* which condenses with formaldehyde (or other aldehydes) to form norharman-3-carboxylic acid, from which norharman can be obtained (*Kermack, Perkin, Robinson,* J. **119**, 1602; *cf. Akabori, Saito,* Ber. **63**, 2245):

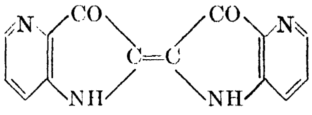
(*1*)


(*2*)


(*3*)


The last synthesis is of interest from the physiological viewpoint, since it is an indication of the course of the synthesis in the plant of the alkaloids of this series.

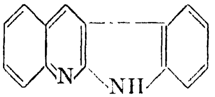
A pyridine ring directly condensed to a pyrrole ring occurs in **pyrindigo**:

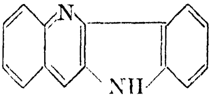


the analogue of indigo in the pyridine series. It is produced from 3-aminopicolinic acid by the same methods used in the synthesis of indigo (*Sucharda*, Ber. **58**, 1724).

2. **QUININDOLINES** (I) and **quindolines** (II) have a quinoline ring fused with an indole ring. They are also known as *peri-* and *ana*-quinindolines, respectively:

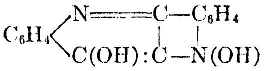
(I)





(II)

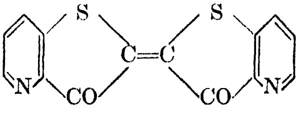
Quinindoline, *peri-quinindoline*, m.p. 343°, is formed by reduction of α-cyano-4,4′-dinitrobibenzyl, $NO_2C_6H_4CH_2CH(CN)C_6H_4NO_2$, with alcoholic ammonium sulfide (p. 236 and *Söderbaum*, Ber. **30**, 3020). An interesting isomerization to *9-quinindolinecarboxylic acid*, yellow, m.p. over 300° (with decarboxylation to quinindoline) occurs when **isoindigo** (p. 84) is treated with alkali (*Friedländer, Sander*, Ber. **57**, 650). Another quinindoline synthesis starts from 2-chloroquinoline (*Lawson, Perkin, Robinson*, J. **125**, 626). The isomeric **quindoline,** *ana-quinindoline*, m.p. 248°, is obtained by condensation of indoxyl or indoxylic acid with *o*-aminobenzaldehyde or by reduction of the **quinindolinediol**:



$$C_6H_4\begin{matrix}\diagup N{=\!=}C-C_6H_4\\ \quad\;\; | \qquad |\\ \diagdown C(OH):C-N(OH)\end{matrix}$$

m.p. over 300°, with HI and phosphorus; the latter compound results from the action of alcoholic sodium hydroxide solution on 4,4′-dinitrobibenzyl-α-malonic ester. **Quindolinecarboxylic acid,** $C_{15}H_9N_2CO_2H$, is prepared by condensation of indoxyl with isatinic acid in alkaline solution or, with intermediate formation of these components, by heating indigo with sodium hydrosulfite and alkali (*Fichter, Rohner*, Ber. **43**, 3489; *Noelting, Steuer*, Ber. **43**, 3512).

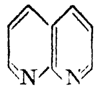
3. For compounds containing a pyridine ring combined with a benzimidazole, indazole, or benzotriazole ring, see *Fries*, Ann. **454**, 121. A bicyclic system of a pyridine and a thiophene ring is the basis of **thiopyrindigo** [*Plazek, Sucharda*, Roczniki Chem. **7** (1927), 187]:



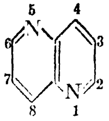
4. The **naphthyridines** contain two pyridine rings fused together. Only the most important of the isomers are mentioned here.

1,8-Naphthyridine (III), gold salt, m.p. 225° (dec.), is formed by reduction of 2,4-dichloro-1,8-dinaphthyridine, which is obtained in turn from **1,8-naphthyridine-2,4-diol,** the product of the condensation of 2-aminonicotinic acid ester and malonic ester (*Koller*, Ber. **60**, 407, 1572). However, the *Skraup* synthesis cannot be applied to 2-aminopyridine (*Seide*, Ber. **59**, 2465). **Octahydro-1,8-naphthyridine,** platinum salt, m.p. 212°, has been synthesized by distillation of *di-(γ-aminopropyl)acetic acid* (*Reissert*, Ber. **27**, 982). Benzo derivatives of 1,8-naphthyridine, called naphthinolines, have been reported (*Reissert*, Ber. **27**, 2244; *Koller, Strang*, Mo. **50**, 144).

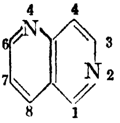
(III)



(IV)



(V)



1,5-Naphthyridine (IV), m.p. 75°, from 3-aminopyridine by the *Skraup* synthesis, and from 3-aminopicolinic acid with phloroglucinol (*Bobranski, Sucharda,* Ber. **60**, 1082).

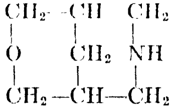
2,5-Naphthyridine (V), benzo derivatives of this naphthyridine have been obtained by the action of *o*-aminobenzaldehyde on 2,4,6-pyridinetriol.

For the preparation of derivatives of the 1,6- and 1,7-*naphthyridines*, see *Fels,* Ber. **37**, 2129; of 2,7-*naphthyridine*, see *Gabriel, Colman,* Ber. **35**, 1358.

(b) Heterocyclic Rings Having C—C—C in Common

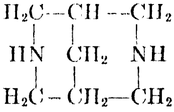
Few examples of this type are known. In **pydine,** 3-*ox*-7-*azabicyclo*[3,3,1]-*nonane* (I), there is a bicyclic combination of a pyrane and a piperidine ring, and in **bispidine,** 3,7-*diazabicyclo*[3,3,1]*nonane* (II), an analogous one of two piperidine rings:

(I)



$$\begin{array}{ccccc} CH_2 & - & CH & - & CH_2 \\ | & & | & & | \\ O & & CH_2 & & NH \\ | & & | & & | \\ CH_2 & - & CH & - & CH_2 \end{array}$$

Pydine



$$\begin{array}{ccccc} H_2C & - & CH & - & CH_2 \\ | & & | & & | \\ HN & & CH_2 & & NH \\ | & & | & & | \\ H_2C & - & CH_2 & - & CH_2 \end{array}$$

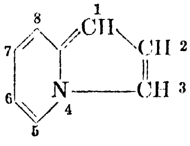
(II)

Bispidine

Derivatives of both ring systems have been synthesized by joining a piperidine ring in the 3,5-position of 4-pyrone or 4-pyridone derivatives with formaldehyde and methylamine (*Mannich, Mohs,* Ber. **63**, 604, 608).

(c) Heterocyclic Rings Having C—N in Common

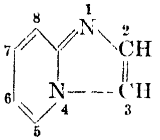
1. **Pyrrocoline,** *indolizine, pyrrolo*[1,2-*a*]*pyridine*:



The parent substance, **pyrrocoline,** m.p. 75° (colorless needles), was first prepared by heating *picolide* (1,3-*diacetylpyrrocoline*) with hydrochloric acid (*Scholtz,* Ber. **45**, 734; *Scholtz, Fraude,* Ber. **46**, 1069). It is also obtained in small yield from 2-picoline and bromoacetaldehyde (*Tschitschibabin,* Ber. **60**, 1616). Pyrrocoline possesses almost no basic properties, but otherwise it is very similar to indole (pine-shaving reaction, condensation with aldehydes and ketones, coupling with diazo compounds). In solution, especially in benzene, pyrrocoline shows a strong violet fluorescence.

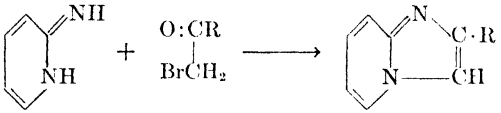
Alkylpyrrocolines are prepared by the action of halogeno ketones on 2-picoline and 2,6-lutidine in good yield: 2-*methyl*-, 2-*phenylpyrrocoline*, m.p. 68°, 215° (*Tschitschibabin,* Ber. **60**, 1614). When pyrrocoline is heated with acetic anhydride and sodium acetate, either 3-*mono*- or 1,3-*diacetylpyrrocoline*, m.p. 176°, is formed, depending on conditions; the latter is identical with picolide, the reaction product of acetic anhydride with 2-picoline (*Tschitschibabin, Stepanow,* Ber. **62**, 1068).

2. **Imidazo**[1,2-*a*]**pyridine, pyrimidazole:**



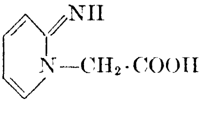
is obtained from 2-aminopyridine, a reaction analogous to the formation of pyrrocoline from 2-picoline:

The imidazopyridine and its alkyl homologues are formed when 2-aminopyridine is heated with halogeno aldehydes or halogeno ketones in a sealed tube; the 2-aminopyridine enters the reaction in its tautomeric form as iminodihydropyridine (*Tschitschibabin*, Ber. **58**, 1704):



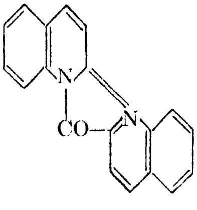
Imidazo[1,2-*a*]pyridine, pyrimidazole, b.p. 153–155° (27 mm.) (*Tschitschibabin*, Ber. **58**, 1706); **2-methylpyrimidazole,** b.p. 148° (20 mm.); **2-phenylpyrimidazole,** m.p. 140° (*Tschitschibabin*, Ber. **59**, 2052).

Oxo derivatives of 2,3-dihydroimidazo[1,2-*a*]pyridine, also known as 2-*pyrimidazolones*, are prepared by the action of chloroacetic acid on 2-aminopyridine (*Reindel*, Ber. **57**, 1381; *Tschitschibabin*, Ber. **57**, 2092). **2-Pyrimidazolone,** m.p. 169°, picrate m.p. 207°, is obtained from the reaction product of chloroacetic acid with 2-aminopyridine, **2-imino-1,2-dihydropyridine-1-acetic acid,** m.p. 250° (dec.):



by boiling with alkali (*Reindel*, Ber. **57**, 1383) or with concentrated hydrochloric acid (*Tschitschibabin*, Ber. **57**, 2097). Pyrimidazolone forms salts with both acids and alkalis. Its methylene group condenses readily with aromatic aldehydes (*Reindel*, *v. Putzer-Reybegg*, Ber. **59**, 2926). Oxidation with potassium ferricyanide in alkaline solution gives a red vat dye, whose constitution is uncertain (*cf. Reindel*, *Rausch*, Ber. **59**, 2921). **2-Pyrimidazole-8-carboxylic acid,** m.p. 220°, from 2-aminonicotinic acid and chloroacetic acid (*Fromm*, *Jokl*, Mo. **44**, 297).

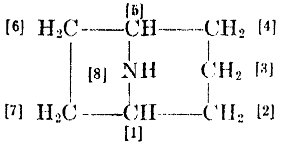
The dye obtained by *Besthorn* from quinaldic acid and acetic anhydride (Ber. **37**, 2371) and also from quinaldic acid chloride and quinoline (Ber. **38**, 2127) has been investigated by *Wieland* (Ber. **61**, 2371), who has assigned it this structure:



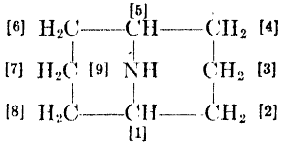
(d) Heterocyclic Rings Having C—N—C in Common

The most important ring systems in this group are **nortropane,** 8-azabicyclo-[3,2,1]**octane, and granatanine,** 9-azabicyclo[3,3,1]nonane, **which are the parent compounds of several important alkaloids.**

Nortropane



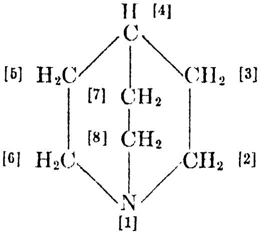
Granatanine



The former contains a pyrrolidine and a piperidine ring, and the latter, two piperidine rings, having the grouping C—N—C in common. For the proof of the constitution of the two ring systems, their most important reactions and their synthesis, see the sections on the related alkaloids: tropane alkaloids, p. 340, and pseudopelletierine, p. 348.

(e) Heterocyclic Rings Having C—C—C—N in Common

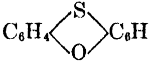
Of the condensed ring systems in which this grouping is shared by two rings, **quinuclidine** must be mentioned:



Quinuclidine, 1-Azabicyclo[2,2,2]octane

It was discovered by *W. Königs* as a constituent of the cinchona alkaloids, quinine and cinchonine. It was synthesized from 4-piperidineëthanol (p. 224). The most important decomposition reactions are treated in connection with the cinchona alkaloids.

II. SIX-MEMBERED RINGS WITH TWO OR MORE HETERO ATOMS

Six-membered rings containing two or more atoms of oxygen or sulfur as ring-members occur in a number of substances which have been described in connection with related compounds. Rings constructed of 4 carbon and 2 oxygen atoms (*o-*, *m-*, and *p-dioxines*) are found in the dialkylene ethers, such as *p-dioxane* (diethylene dioxide), and in the anhydrides of α-hydroxy carboxylic acids, such as *diglycolide* (2,5-*p*-dioxanedione) and *diglycolic anhydride* (2,6-*p*-dioxanedione). Condensation of formaldehyde with nitrophenols produces derivatives of 1,3-*benzodioxane* [*Chattaway, Calvert,* Anal.soc.esp.fís.quím. **26** (1928), 417]. Two sulfur atoms are contained in the six-membered ring of *p-dithiane* (diethylene sulfide) and of *thianthrene* (di-*o*-phenylene disulfide) (*Fries, Engelbertz,* Ann. **407,** 194; *Fries, Koch, Stukenbrock,* Ann. **468,** 162). *Phenoxathiin,*  $C_6H_4{<}\overset{S}{\underset{O}{}}{>}C_6H_4$, has an O- and an S-atom in its ring (*Drew,* J. **1928,** 506); *phenoxaselenin* (*Drew,* J. 1928, 511) and *phenoxatellurin* (*Drew, Thomason,* J. **1927,** 116) are similarly formed with an O- and an Se- or Te-atom. The compounds produced by the polymerization of aldehydes and thioaldehydes, such as *trioxymethylene* (*s*-trioxane), *trithiomethylene* (*s*-trithiane), and *paraldehyde* (*cf.* p. 3 ff.), have 3 O-atoms or 3 S-atoms in their rings.

AZINES*

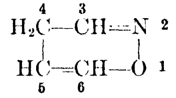
As in the five-membered rings, those six-membered rings in which nitrogen occurs among the two or more hetero atoms merit more consideration. Their formulas can be derived from the furan, thiophene and pyrrole rings by replacement of the methine groups (see p. 89 for an analogous derivation of the azoles), and they are known collectively as azines. A schematic summary of the six-membered rings containing two or more hetero atoms has been given from this point of view in the introduction (p. 6).

Six-membered rings with the hetero atoms: N and O, 2 N and O, 2 N and 2 O are called oxazines, oxadiazines (azoxazines), and dioxadiazines; those with N and S, and 2 N and S, are called thiazines and thiadiazines, while those containing 2, 3, and 4 N-atoms are known as diazines, triazines, and tetrazines. Position isomers of azines containing two hetero atoms are distinguished by the symbols *o*-, *m*-, and *p*-, or by numbers, according to the position of the hetero atoms; e.g., *m*-oxazine = 1,3-oxazine. For the numbering of heterocyclic rings in general, see p. 8.

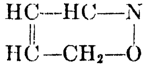
SIX-MEMBERED RINGS WITH TWO HETERO ATOMS

1. OXAZINES

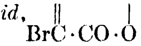
(a) The ring of 1,2-**oxazine**, or *o*-**oxazine**:

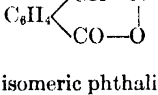


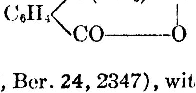
1,2,4-Oxazine,
4-Methylene form of *o*-oxazine



1,2,6-Oxazine,
6-Methylene form of *o*-oxazine

This ring occurs in the oxime anhydrides of the γ-aldehyde and γ-ketone carboxylic acids, such as the *oxime anhydride of mucobromic acid*,  $\begin{matrix} \text{BrC·CH:N} \\ \| \quad\quad | \\ \text{BrC·CO·O} \end{matrix}$ (*Bistrzycki, Simonis*, Ber. **32**, 536), and the *oxime anhydride of β-benzylidenelevulinic acid*, which bear the same relation to the oxime anhydrides of the δ-oxo carboxylic acids, the isoxazolones, (p. 120), as the δ-lactones do to the γ-lactones (*Dolfuss*, Ber. **25**, 1930). The ring closure of the oximes of *o*-formylbenzoic acid and *o*-acylbenzoic acids takes place without difficulty, producing derivatives of 2,3,1-benzoxazine: 2,3,1-**benzoxazin**-1-**one** (I), from phthalaldehydic acid, rearranges

(I) 

 (II)

readily to the isomeric phthalimide (*Allendorff*, Ber. **24**, 2347), with intermediate formation of *o*-cyanobenzoic acid (*cf.* indoxazenes, p. 122). 4-**Methyl**-2,3,1-**benzoxazin**-1-**one** (II), m.p. 179° (*Gabriel*, Ber. **16**, 1995).

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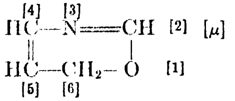
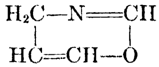
* *Fierz-David:* Künstliche organische Farbstoffe (Springer, Berlin, 1926).

(b) The 1,3- or *m*-**oxazine** ring:

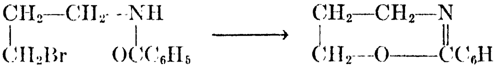


1,3,6-Oxazine,
6-Methylene form of *m*-oxazine



1,3,4-Oxazine,
4-Methylene form of *m*-oxazine

a. **Pentoxazolines,** or **5,6-dihydro-1,3,4-oxazines,** are prepared from γ-bromoalkylamides by elimination of HBr, which is analogous to the formation of oxazolines (p. 137) from β-bromoalkylamides (*Gabriel, Elfeldt,* Ber. **24,** 3213):

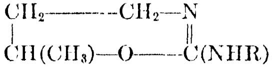


N-γ-Bromopropylbenzamide

2-Phenyl-5,6-dihydro-1,3,4-oxazine

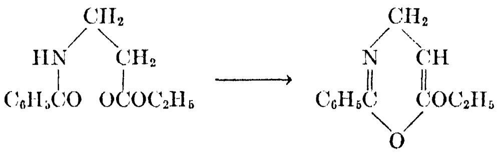
2-Phenyl-6-methyl-5,6-dihydro-1,3,4-oxazine and **2-phenyl-4,4-6-trimethyl-5,6-dihydro-1,3,4-oxazine,** m.p. 32°, are obtained from γ-chlorobutyl- and γ-bromoisohexylbenzamide (*cf.* p. 277).

2-Allylamino- and **2-phenylamino-6-methyl-5,6-dihydro-1,3,4-oxazine,** or N-*allyl-* and N-*phenylbutylene-pseudourea:*



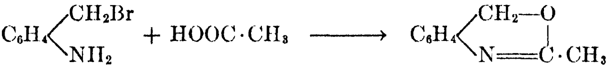
from γ-chlorobutylamine with allyl and phenyl isothiocyanate (*Luchmann,* Ber. **29,** 1428; *Kahan,* Ber. **30,** 1319).

Acyl derivatives of β-amino carboxylic acids, when digested for a long time with P_2O_5 or PCl_5, yield 2-hydroxy-6-alkyl-1,3,4-oxazines (*Karrer, Miyamichi,* Helv. **9,** 336). The following equation shows this ring closure for N-benzoyl-β-aminopropionic acid:



By a similar reaction γ-chloropropylurethans are converted by alkali to derivatives of tetrahydro-1,3-oxazine (*Dox, Yoder,* Am. **45,** 723).

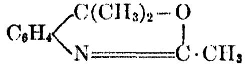
b. **3,1,4-Benzoxazine** derivatives are formed from *o*-aminobenzyl halides with acid anhydrides (*Gabriel, Posner,* Ber. **27,** 3515; *Auwers,* Ber. **37,** 2249):

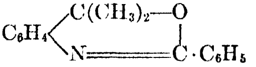


o-Aminobenzyl bromide

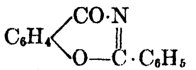
2-Methyl-3,1,4-benzoxazine

This group also includes the **coumazonic acids** (*Widmann,* Ber. **16,** 2585), such as 2,4,4-trimethyl-3,1,4-benzoxazine, 2-*methylcoumazonic acid* (I), m.p. 218°, and **2-phenyl-4,4-dimethyl-3,1,4-benzoxazine** (II), m.p. 220°, which are obtained from 3-amino-4-(hydroxypropyl)-benzoic acid with acetyl chloride and benzoyl chloride, with simultaneous decarboxylation.

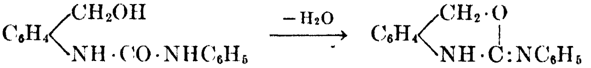
(I) 

 (II)

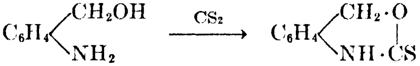
Acylanthranils are 3,1,4-benzoxazines.

2-Phenyl-1,3,4-benzoxazone, , m.p. 106°, results from the action of gaseous HCl on O- and N-benzoylsalicyclic acid amide (*Titherley,* J. **97,** 200).

The **imido-** and **thiocoumazones** are 2-imino- and 2-thio-1,2-dihydro-3,1,4-benzoxazines; the former are obtained from the urea derivatives of *o*-aminobenzyl alcohol by elimination of water, and the latter, from *o*-aminobenzyl alcohol and similar substances in alcoholic solution by treatment with CS_2:



2-Phenylimino-1,2-dihydro-3,1,4-benzoxazine

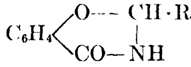


2-Thiono-1,2-dihydro-3,1,4-benzoxazine

The iminodihydrobenzoxazines are isomeric with the oxotetraquinazolines; when warmed with aromatic amines they are converted to quinazoline derivatives (p. 295), the oxygen in the ring being replaced by the group NR. The thiodihydrobenzoxazines behave similarly (*Paal, Vanvolxem,* Ber. **27,** 2424).

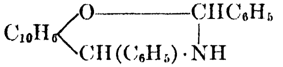
2-Phenylimino-1,2-dihydro-3,1,4-benzoxazine, *phenylimidocoumazone,* $C_8H_7ON{:}(NC_6H_5)$, m.p. 146° (*Söderbaum, Widman,* Ber. **22,** 2938), forms stable salts with acids, and addition products with carboxylic acid anhydrides and chlorides. **2-Thiono-1,2-dihydro-3,1,4-benzoxazine** *thiocoumazone,* $C_8H_7ON{:}S$, m.p. 142°, is an acid, and forms a sparingly soluble potassium salt (*Paal, Laudenheimer,* Ber. **25,** 2979; *Paal, Commerell,* Ber. **27,** 1866).

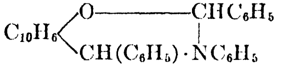
2-Methyl- and **2-phenyl-2,3-dihydro-1,3,4-benzoxaz-4-one:**



m.p. 146° and 169°, are prepared by the condensation of acetaldehyde and benzaldehyde with salicylamide (*Titherley,* J. **91,** 1419).

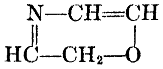
3,4-Dihydro-2-naphth[2,1-*e*]-*m*-**oxazines** are formed by the condensation of 2-naphthols with aldehydes, NH_3, or amines (*Betti,* Gazz. **31,** II, 170):





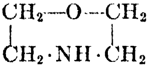
The heterocyclic ring of 2-isonitroso-3(2)-benzofuranone is enlarged under the conditions of the Beckmann rearrangement, and 1,3,4-benzoxazine-2(3),4-dione is formed (*Mameli,* Atti.cong.naz.chim.pura applicata, 1st Congr. **1923,** 426; C. **1924, I,** 2517).

(c) 1,4-Oxazines, *p*-oxazines:

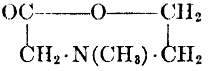


(*1*) Only hydrogenated derivatives of the simple nucleus are known. **Morpholine,** *tetrahydro*-1,4-*oxazine* (see below), b.p. 129°, was given this name because for a long time morphine (p. 358) was assumed to contain a similar ring. It is obtained from 2,2′-iminodiethanol, $NH(CH_2CH_2OH)_2$, (Vol. I, p. 380) by heating with 70% sulfuric acid at 160–170°, or, in better yield, from the di-2-naphthyl ether of N-toluenesulfonyl-2,2′-iminodiethanol, $(C_{10}H_7OCH_2CH_2)_2$-$NSO_2C_7H_7$, which is prepared from the β-bromoethyl ether of 2-naphthol with toluenesulfamide, by heating with mineral acids (*Marckwald, Chain,* Ber. **34,** 1157). Morpholine is similar to piperidine. By the decomposition of its methyl iodide addition product, it gives trimethylamine, acetylene and water (*Knorr,* Ann. **301,** 1; *Knorr, Mathes,* Ber. **32,** 736). The picrate is sparingly soluble in water. For nitroso- and aminomorpholine, see *Knorr,* Ann. **301,** 6.

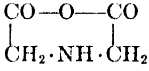
The oxo derivatives of morpholine include 4-**methylmorpholone**, b.p. 233°, obtained from N-hydroxyethyl-N-methylglycine (*Knorr*, Ann. **307**, 199), **diglycolic acid imide** and the isomeric **diglycolamic acid anhydride** (Vol. I, p. 431):


$$\begin{array}{l} CH_2—O—CH_2 \\ |\qquad\quad | \\ CH_2·NH·CH_2 \end{array}$$

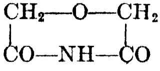
Morpholine


$$\begin{array}{l} OC———O———CH_2 \\ |\qquad\qquad\qquad | \\ CH_2·N(CH_3)·CH_2 \end{array}$$

4-Methylmorpholone


$$\begin{array}{l} CO—O—CO \\ |\qquad\quad | \\ CH_2·NH·CH_2 \end{array}$$

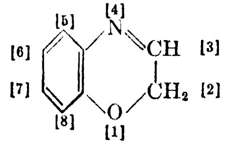
Diglycolamic acid anhydride

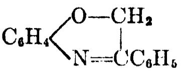

$$\begin{array}{l} CH_2—O—CH_2 \\ |\qquad\quad | \\ CO—NH—CO \end{array}$$

Diglycolic acid imide

(*2*) The following compounds are derived from 1,4,2-**benzoxazine** (I): 3-**Phenyl-1,4,2-benzoxazine** (II), m.p. 103°, which is formed by reduction of *o*-nitrophenyl phenacyl ether, $(NO_2)C_6H_4OCH_2COC_6H_5$; **3-methyl-1,4,2-benzoxazine**, similarly obtained from *o*-nitrophenoxyacetone. Stronger reduction of the phenoxyacetone produces 3-**methyl-3,4-dihydro-1,4,2-benzoxazine**, 3-*methylbenzomorpholine*, $C_9H_{11}NO$, b.p. 255° (*Stoermer, Franke*, Ber. **31**, 752).

(I)

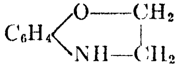



$$C_6H_4\left\langle\begin{array}{l} O—CH_2 \\ \quad\ | \\ N{=}CC_6H_5 \end{array}\right.$$

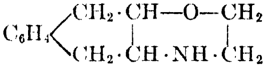
(II)

3,4-**Dihydro-1,4,2-benzoxazine**, *benzomorpholine* (III), b.p. 268°, obtained from *o*-β-hydroxyethylaminophenol (*Knorr*, Ber. 22, 2095; *cf*. *Fairbourne, Toms*, J. **119**, 2076), is converted by exhaustive methylation to the vinyl ether of *o*-dimethylaminophenol, $(CH_3)_2NC_6H_4O·CH{:}CH_2$. It is similar to tetrahydroquinoline (*Knorr*, Ber. **32**, 732).

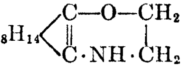
(III)


$$C_6H_4\left\langle\begin{array}{l} O——CH_2 \\ \qquad\quad | \\ NH—CH_2 \end{array}\right.$$

(IV)


$$C_6H_4\left\langle\begin{array}{l} CH_2·CH—O—CH_2 \\ \qquad\ \ |\qquad\quad | \\ CH_2·CH·NH·CH_2 \end{array}\right.$$

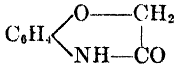
(V)

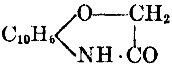

$$C_8H_{14}\left\langle\begin{array}{l} C—O—CH_2 \\ \| \qquad\quad | \\ C·NH·CH_2 \end{array}\right.$$

The reaction of tetrahydronaphthalene oxide with hydroxyethylamine yields **naphthalanmorpholine**, 2,3,4a,5,10,10a-*hexahydro-4-naphth*[2,3]-*p-oxazine* (IV), m.p. 63°, b.p. 312°, which, like morphine, is a soporific. Exhaustive methylation converts it to the β-dimethylaminoethyl ether of dihydronaphthol, $C_{10}H_9O·CH_2CH_2·N(CH_3)_2$, which can be split more readily than methylmorphimethine (p. 259) into naphthaline and dimethylaminoethanol (*Knorr*, Ber. **32**, 742; Ann. **307**, 171). Aminocamphor and ethylene oxide condense to give **camphanomorpholine** (V), b.p. 242° (*Duden*, Ann. **307**, 187).

1,4,2-**Benzoxaz-3(4)-one**, *benzo-3-morpholone* (VI), from *o*-nitrophenoxyacetic acid (*Wheeler, Barnes*, Am.Chem.J. **20** (1898), 555). The two isomers: **2-methyl-1,4,2-benzoxaz-3(4)-one** and **3,4-dihydro-3-methyl-1,4,2-benzoxaz-2-one**, m.p. 145° and 110°, are prepared from *o*-nitrophenoxypropionic acid and from *o*-aminophenol with bromopropionic acid ester (*Bischoff*, Ber. **30**, 2927; **33**, 1598). 1-**Naphth**[2,1]-*p*-**oxaz-2(3)-one**, *naphtho-2-morpholone* (VII), m.p. 216°. By electrolytic reduction the morpholones are partially converted to morpholines and partially decomposed to carbocyclic compounds (*Lees, Shedden*, J. **83**, 750).

(VI)

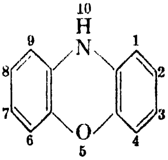

$$C_6H_4\left\langle\begin{array}{l} O——CH_2 \\ \qquad\quad | \\ NH—CO \end{array}\right.$$


$$C_{10}H_6\left\langle\begin{array}{l} O——CH_2 \\ \qquad\quad | \\ NH·CO \end{array}\right.$$

(VII)

(*3*) Among the derivatives of **phenoxazine** (**dibenzo-*p*-oxazine**), **benzophenoxazine**, and **dibenzophenoxazine** are a number of important dyes.

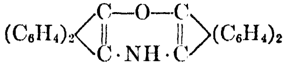
Phenoxazine, m.p. 148°.



is prepared by heating *o*-aminophenol with pyrocatechol (*Kehrmann,* Ann. **322,** 9). N-Acetylphenoxazine, m.p. 142°.

3-**Methylphenoxazine,** m.p. 124°, from pyrocatechol and *o*-amino-*m*-cresol; 3,6-**dimethylphenoxazine,** m.p. 205°, from homopyrocatechol and *o*-amino-*m*-cresol. 4-**Nitrophenoxazine,** m.p. 166°, is prepared from 2,4-dinitro-2′-hydroxydiphenylamine by warming with dilute aqueous sodium hydroxide, HNO_2 being eliminated (*Ullmann,* Ann. **366,** 80). 2,4-**Dinitrophenoxazine** is similarly obtained from picryl chloride and *o*-aminophenol.

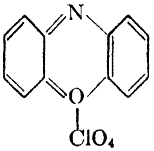
18-**Tetrabenzo**[*a,c,h,j*]**phenoxazine, phenanthroxazine:**



$$(C_6H_4)_2\left\langle\begin{array}{c} C-O-C \\ \| \qquad \| \\ C\cdot NH\cdot C \end{array}\right\rangle(C_6H_4)_2$$

from 9,10-dihydroxyphenanthrene with NH_3 (*Bamberger, Grob,* Ber. **34,** 535).

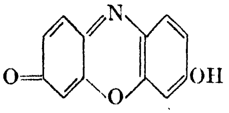
Phenoxazine and its homologues are oxidized by bromine or ferric chloride or H_2O_2 in acid solution to colored, *ortho*-quinoid azoxonium salts (with tetravalent oxygen); *meri*-quinoid compounds are formed as intermediate products. These *o*-quinoid oxonium salts are very unstable; several have been isolated as perchlorates (*Kehrmann, Boubis,* Ber. **50,** 1662):



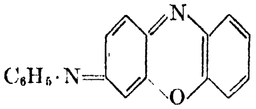
Phenoxazonium perchlorate, brownish crystals; explosive

The phenoxazonium salts are very reactive substances. They add aromatic amine as the quinones do; this permits the introduction of RHN-groups in the position *para* to the nitrogen. Phenoxazonium compounds can be hydroxylated by treatment with alkali.

The products obtained by these two reactions are the **phenoxazine dyes,** which are not derived from the *o*-quinoid phenoxazonium structure, but from the *p*-quinoid **phenoxazone** or **phenoxazime:**



Hydroxyphenoxazone (resorufin)



Phenylphenoxazime

Conclusive evidence for this interpretation of the structure of the phenoxazone and phenoxazime dyes is their complete absorption, in contrast to the phenoxazonium salts (*cf. Kehrmann, Sandoz,* Ber. **50,** 1667).

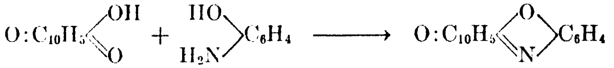
These dyes are analogous to the simplest indophenols and indamines (Vol. III, pp. 245, 109):

$$O{:}C_6H_4{:}N\cdot C_6H_4OH \qquad HN{:}C_6H_4{:}N\cdot C_6H_4NH_2$$

They differ from these only in the addition of the 1,4-oxazine ring.

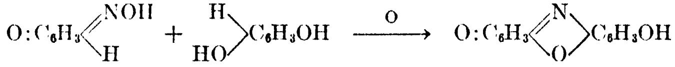
The phenoxazine dyes are prepared by the following methods:

(*1*) From *o*-hydroxyquinones and *o*-hydroxyquinonimines by condensation with *o*-aminophenols. The hydroxy-*p*-quinones of the naphthalene series are particularly suited to this condensation (*Kehrmann, Messinger*, Ber. **26**, 2375; *Kehrmann*, Ber. **28**, 353):



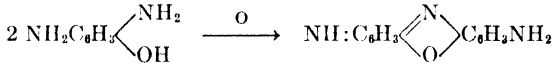
2-Hydroxy-1,4-naphthoquinone   *o*-Amino-phenol   5-Benzo[*a*]phenoxazone

(*2*) Condensation of dichloroquinonimines, nitrosophenols, or nitrosodimethylaniline with polyhydric phenols or tertiary aminophenols produces hydroxyl and amino derivatives of phenoxazones and phenoxazimes, which are the real dyes:



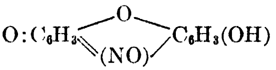
Nitrosophenol   Resorcinol   7-Hydroxy-3-phenoxazone, Resorufin

(*3*) Aminophenoxazimes are obtained by oxidation of hydroxy-*p*-phenylenediamines in glacial acetic acid by air (*Nietzki, Becker*, Ber. **40**, 3397; *Kehrmann, Poplawski*, Ber. **42**, 1275):



3-Phenoxazone, $O:C_6H_3(NO)C_6H_4$, m.p. 217°, golden brown flakes (*Kehrmann, Cherpillod*, Helv. **7**, 973). Phenoxazine is converted by $FeCl_3$ to an unstable phenoxazonium chloride (see above), which yields phenoxazone when boiled with water (*Kehrmann, Saager*, Ber. **35**, 341).

RESORUFIN, **7-hydroxy-3-phenoxazone**, $OC_6H_3(NO)C_6H_3(OH)$, is prepared by the action of nitric acid containing nitrous acid on an ethereal solution of resorcinol (*Weselsky*, Ann. **162**, 273), and also by the reaction of nitrosoresorcinol with resorcinol (*Nietzki*, Ber. **24**, 3366). **Resazurin**:



occurs as an intermediate product. The solutions of resorufin in alkalis are rose-red with a magnificent cinnabar-red fluorescence. **Orcirufin** is formed, similarly to resorufin, from orcinol. 3,6-**Dimethylresorufin**, bright red needles (*Henrich, Götz*, Ber. **58**, 1055).

N-Phenyl-3-phenoxazime, $C_6H_5N[3]C_6H_3(NO)C_6H_4$, red flakes, m.p. 197°, from phenoxazine by oxidation with $FeCl_3$ in the presence of aniline salts, is converted by further treatment with aniline into N-phenyl-6-anilino-3-phenoxazime, $C_6H_5N[3]C_6H_3(NO)C_6H_3[6]NHC_6H_5$, which is similar to the dyes of the **capri blue** type. The latter are derived from 3,6-diaminophenoxazine, *e.g.*, $(CH_3)_2N$-$C_6H_3(NO)C_6H_2(CH_3)N(C_2H_5)_2$, whose zinc chloride double salt, from *o*-diethylamino-*m*-cresol and nitrosodimethylaniline, is marketed as capri blue GON [*Möhlau, Klimmer, Kahl*, Z.Farb.Textilchemie **1** (1902), 354].

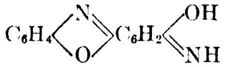
Gallocyanine, $(CH_3)_2NC_6H_3(NO)C_6H(OH)(CO_2H)O$, *dimethylaminohydroxyphenoxazonecarboxylic acid*, is prepared from gallic acid with nitrosodimethylaniline, and forms with mordants, especially chromic oxide, stable violet *lakes* (for calico printing). When heated with aqueous sodium acetate, soda, or the like, gallocyanine is decarboxylated to dimethylaminohydroxyphenoxazone (Ger. Pat. 192971, 1906). For the products of the reaction of gallocyanine dyes with primary aromatic amines, see *Grandmougin, Bodmer*, J.pr. **77**, 498.

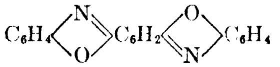
Chlorohydroxyphenoxazone, $C_6H_4(NO)C_6HCl(OH):O$, m.p. 235° (dec.), from *p*-dihydroxychloroquinone with aminophenol (*Kehrmann, Messinger*, Ber. **26**, 2375).

5-**Benzo[*a*]phenoxazone**, $O:C_{10}H_5(NO)C_6H_4$, m.p. 192° (synthesis: p. 276). 9-**Benzo[*a*]phenoxazone**, $O:C_6H_3(NO)C_{10}H_6$, brown needles, m.p. 211°, from nitrosophenol and 2-naphthol (*Fischer, Hepp*, Ber. **36**, 1807). 5-**Benzo[*a*]-phenoxazime**, $NH:C_{10}H_5(NO)C_6H_4$, m.p. 243°, from hydroxynaphthaquinonimine (Vol. III, p. 633) with *o*-aminophenol.

N,N-Dimethyl-9-benzo[*a*]phenoxazime chloride, $C_{10}H_6(NO)C_6H_3N(CH_3)_2Cl$, from 2-naphthol with nitrosodimethylaniline hydrochloride in alcoholic solution, is naphthol blue (*meldola blue*) which dyes cotton mordanted with tannin violet-blue (*Witt*, Ber. **23**, 2247). Nile blue is an amino derivative of naphthol blue, and cyanamine is an anilino derivative.

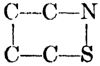
Hydroxyphenoxazime (I), obtained by oxidation of *o*-aminophenol, condenses with another mol of *o*-aminophenol to **triphenodioxazine** (II), dark violet, sublimable needles. The latter is also formed directly from *o*-aminophenol by oxidation by the air (*Seidel*, Ber. **23**, 182; *Fischer, Jonas*, Ber. **27**, 2784; *Krause*, Ber. **32**, 126). For methyltriphenodioxazine, see *Kehrmann, Bürgin*, Ber. **29**, 2076.

(I) 

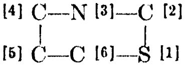
 (II)

PHENOXARSINE. For the synthesis of derivatives of phenoxarsine, which is analogous to phenoxazine, see *Roberts, Turner*, J. **127**, 2004.

2. THIAZINES

(a) 1,2-Thiazines: 

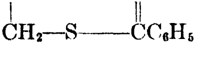
At the present time no compounds having this structure are known.

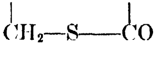
(b) 1,3-Thiazines: 

The following compounds contain 1,3-thiazine rings:

1. The **penthiazolines**, corresponding to the pentoxazolines (p. 272), are **5,6-dihydro-1,3,4-thiazines**. They are prepared from γ-halogenoalkylthiobenzamides.

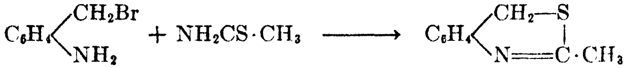
2-Phenyl-5,6-dihydro-1,3,4-thiazine, **2-phenylpenthiazoline** (I), m.p. 45°, is obtained from thiobenzamide with 1-bromo-3-chloropropane (*Pinkus*, Ber. **26**, 1077). **2-Phenyl-4,4,6-trimethyl-5,6-dihydro-1,3,4-thiazine**, $C_4H_3NS(CH_3)_3(C_6H_5)$, m.p. 34°, from γ-bromoisohexylthiobenzamide. **6-Methyl-5,6-dihydro-1,3,4-thiazine-2-thiol** and **4,4,6-trimethyl-5,6-dihydro-1,3,4-thiazine-2-thiol**, m.p 131° and 180°, are prepared from γ-chlorobutylamine and γ-bromoisohexylamine with carbon disulfide [*Luchmann*, Ber. **29**, 1429; *Kahan*, Ber. **30**, 1321; *cf. Dixon*, J. **69**, 851; *Gadamer*, Arch.Pharm. **234** (1896), 1].

(I) 

 (II)

Tetrahydro-1,3,4-thiazine-2,4-dione, **dioxopenthiazolidine**, *sinapanpropionic acid* (II), m.p. 159°, is formed from xanthamide with β-iodopropionic acid (*Langlet*, Ber. **24**, 3848).

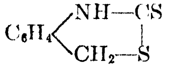
2. Derivatives of **3,1-benzothiazine** (*phenpenthiazole*) result from the condensation of *o*-aminobenzyl halides with amides of thiocarboxylic acids (*Gabriel, Posner*, Ber. **27**, 3519):

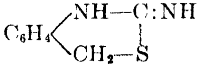


2-Methyl-3,1,4-benzothiazine, m.p. 46°, is prepared from 2-methyl-3,1,4-benzoxazine with P_2S_5, from *o*-acetylaminobenzyl alcohol with P_2S_5, and from *o*-

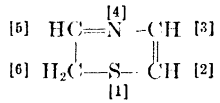
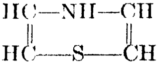
acetylaminobenzyl sulfide with PCl_5. For other derivatives, see *Kippenberg*, Ber. **30**, 1143.

The **imino- and thio-1,2-dihydro-3,1,4-benzothiazines** (imino- and thiocoumothiazones) are prepared, similarly to the corresponding benzoxazines (imino- and thiocoumazones, p. 273), from thiourea derivatives of *o*-aminobenzyl alcohol or from aminobenzyl alcohols with CS_2 and alcoholic KOH. **2-Thio-1,2-dihydro-3,1,4-benzothiazine**, *thiocoumothiazone* (III), m.p. 166°, is an acid; when digested with aniline it gives 2-thiotetrahydroquinazoline, the sulfur atom in the ring being replaced by an NC_6H_5-group (*cf.* p. 273 and 295). **2-Imino-**

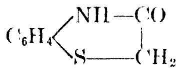
(III) 

 (IV)

1,2-dihydro-3,1,4-benzothiazone, *iminocoumazone* (IV), m.p. 137°, from *o*-nitrobenzyl thiocyanate by reduction, and from *o*-aminobenzyl chloride and thiourea, is oxidized by permanganate to 4(3)-quinazolone (p. 293). When heated with aniline it gives 2-phenylimino-1,2-dihydro-3,1,4-benzothiazine, m.p. 197°, which is also formed by elimination of water from 1-α-hydroxytolyl-3-phenylthiourea, $HOCH_2 \cdot C_6H_4NHCSNHC_6H_5$ (*Söderbaum, Widman*, Ber. **22**, 2933; *Paul, Commerell*, Ber. **27**, 2429).

(c) **1,4-Thiazine**:  or 

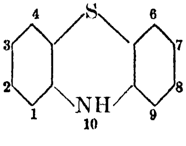
1. One of the benzo derivatives of this ring is **benzo-1,4,2-thiazin-2(3)-one**:



m.p. 179°, which is obtained from *o*-aminobenzenethiol and bromoacetic acid (*Unger*, Ber. **30**, 607; *Unger, Graff*, Ber. **30**, 2389). For 2-mono- and 2,2-dihalogen derivatives of this compound, see *Zahn*, Ber. **56**, 578. The 2,2-dihalogen derivative suffers a ring shrinkage when digested with alcohol, yielding benzothiazole-2-carboxylic acid ester (*Zahn*, Ber. **56**, 578).

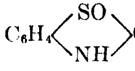
The symmetrical dibenzo derivatives, **phenothiazines** and **dibenzophenothiazines** (*thiodiphenylamines* and *thiodinaphthylamines*) are more important. Phenothiazine corresponds to phenoxazine or dibenzo-*p*-oxazine (p. 274) and, like it, numbers a series of important dyes among its derivatives. One of these is the valuable methylene blue.

2. **PHENOTHIAZINE, thiodiphenylamine**:



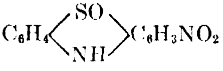
m.p. 180°, b.p. 370°, is obtained from *o*-aminobenzenethiol with pyrocatechol at 220°, as phenoxazine is formed from *o*-aminophenol and pyrocatechol. It is more readily prepared by heating diphenylamine with sulfur, especially in the presence of a trace of iodine (*Kehrmann, Dardel*, Ber. **55**, 2348). It is a neutral substance, and its imine hydrogen can be replaced by alkyl groups (N-methyl derivative, m.p. 99°; *Kehrmann, Zybs*, Ber. **52**, 131; *Kehrmann, Sandoz*, Ber. **50**, 1676) and by acid radicals (N-acetyl derivative, m.p. 197°). With dimethyl sulfate it forms S-alkylsulfonium compounds, which crystallize as the perchlorates (*Kehr-*

mann, Dardel, Ber. **55,** 2346). When boiled over copper phenothiazine is converted into carbazole (a ring shrinkage). For the qualitative detection of its presence, see the section on thionine. **Tetrachlorophenothiazine,** m.p. 235° (*Unger, Hofmann,* Ber. **29,** 1363). Hydrogen peroxide oxidizes phenothiazine to **phenothiazine 5-oxide,** *diphenylamine sulfoxide* (I), m.p. 250°, which reacts with cold hydrochloric acid to give phenazothionium chloride (see below), and with hot hydrochloric acid to give chlorophenothiazine (*Barnett, Smiles,* J. **95,** 1253; *Page, Smiles,* J. **97,** 1112). With nitric acid it forms nitrophenothiazine 5-oxide (II), which reduces to 2-**aminophenothiazine,** and dinitrophenothiazine 5-oxide, which reduces to 2,8-**diaminophenothiazine,** *leucothionine* (III). The latter is



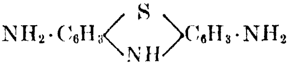
$C_6H_4{<}\overset{SO}{\underset{NH}{}}{>}C_6H_4$

(I)



$C_6H_4{<}\overset{SO}{\underset{NH}{}}{>}C_6H_3NO_2$

(II)



$NH_2\cdot C_6H_3{<}\overset{S}{\underset{NH}{}}{>}C_6H_3\cdot NH_2$

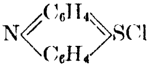
(III)

also produced when diaminodiphenylamine, $(NH_2C_6H_4)_2NH$, is heated with sulfur. It is the leuco-base of the simplest thionine dye, into which it is converted by oxidation with $FeCl_3$. The tetramethyl derivative of leucothionine is the leuco-base of methylene blue (p. 280). The therapeutically active acyl derivatives of leuco-methylene blue, such as $N(CH_3)_2C_6H_4[N(COCH_3)S]C_6H_4N(CH_3)_2$, are obtained from its zinc chloride double salt with acid chlorides (*Cohn,* Ber. **33,** 1567).

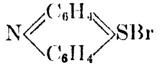
1,3-**Dinitrophenothiazine,** from picryl chloride and *o*-aminobenzenethiol, yields an isomer of leuco-thionine when reduced (*Kehrmann,* Ann. **322,** 57; *Kehrmann, Steinberg,* Ber. **44,** 3011).

12-**Benzo**[*a*]- and **benzo**[*b*]**phenothiazine,** *thiophenyl-α-* and *β-naphthylamine,* $C_6H_4(SNH)C_{10}H_6$, m.p. 130.5° (*Kehrmann, Christopoulus,* Ber. **54,** 649) and 178°, from N-phenyl-1- and 2-naphthylamine with sulfur. 14-**Dibenzo**[*a,j*]-**phenothiazine** and 7-**dibenzo**[*c,h*]**phenothiazine,** thio-*α*- and *β*-dinaphthylamine, $S(C_{10}H_6)_2NH$, m.p. 177° and 236°, from 1,1′- and 2,2′-dinaphthylamine with sulfur (*Kehrmann,* Ann. **322,** 44, 51; *Kehrmann, Christopoulus,* Ber. **54,** 655).

Like phenoxazine (p. 275), phenothiazine and its homologues are converted by oxidation with $FeCl_3$ or bromine into colored, ortho-quinoid azothionium salts (with tetravalent sulfur):



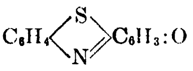
$N{<}\overset{C_6H_4}{\underset{C_6H_4}{}}{>}SCl$



$N{<}\overset{C_6H_4}{\underset{C_6H_4}{}}{>}SBr$

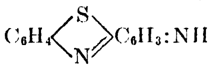
which are generally isolated as the perchlorates and which, like the azoxonium salts, are substituted in the para-position to the N-atom by NHR- or OH-groups when treated with amines or water.

For the structure of the **thiazine dyes** so formed the same conclusions are valid as for that of the phenoxazine dyes. The dye bases are derivatives of the *p*-quinoid *phenothiazone* and *phenothiazime* (see formulas). They are therefore structurally related to the indophenols and indamines, which, indeed, may be assumed to be present as intermediate products in the preparation of these dyes (see methylene blue). The most conclusive evidence for their formulation as *p*-quinonimines or *p*-diimines is provided by the extensive data on the absorption spectra of the dyes in this series (summary: *Kehrmann,* Ann. **414,** 149).



$C_6H_4{<}\overset{S}{\underset{N}{}}{>}C_6H_3{:}O$

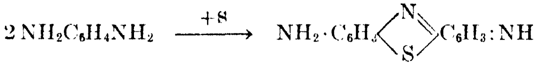
Phenothiazone



$C_6H_4{<}\overset{S}{\underset{N}{}}{>}C_6H_3{:}NH$

Phenothiazime

Among the phenothiazimes are Lauth's dyes, so named after *Lauth,* who first prepared them; their constitution as derivatives of 7-aminophenothiazimes was established by *Bernthsen* (Ann. **230,** 73; **251,** 1). They are obtained by oxidation of *p*-phenylenediamines in the presence of H_2S, indamines being formed as intermediate products (see methylene blue):



Another method for the preparation of these dyes depends on the reaction of indamines with thiosulfuric acid, yielding thiosulfonic acids, which are converted to the leuco-bases of the thiazine dyes by digestion with dilute acids. The dyes can therefore be obtained by the oxidation of a mixture of 1 mol *p*-diamine with 1 mol monoamine, which form indamines, in the presence of thiosulfate.

Phenothiazones are formed by oxidation of *p*-aminophenols in the presence of H_2S.

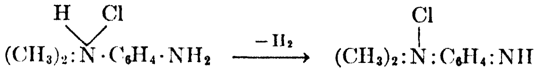
Phenothiazime, *3-imino-3-isophenothiazine,* $C_6H_4(NS)C_6H_3NH$ (red-brown needles), is obtained by oxidation of 2-aminophenothiazine (p. 279), by deamination of thionine (see below) or by the action of alcoholic ammonia on phenazothionium perbromide (*Kehrmann,* Ber. **49,** 2831). It reacts with amines without heat to form N-alkylated thionines: $NHRC_6H_3(NS)C_6H_3NH$ (*Kehrmann, Schaposchnikoff,* Ber. **33,** 3291). The phenothiazime chloride, *2-aminophenazothionium chloride* (see above), can be diazotized in strongly acid solution (*Kehrmann,* Ann. **322,** 64). For *benzo*[*a*]*phenothiazines,* see *Kehrmann, Christopoulos,* Ber. **54,** 651.

N-Phenylphenothiazime, $C_6H_4(NS)C_6H_3(NC_6H_5)$, dark red flakes, m.p. 150°, from phenothiazine by oxidation with $FeCl_3$ in the presence of aniline salt; its chloride, *2-anilinophenazothionium chloride,* is converted on further treatment with aniline to 2,8-dianilinophenazothionium chloride or diphenylthionine chloride (*Kehrmann,* Ann. **322,** 39).

7-Aminophenothiazime, thionine, *Lauth's violet,* $NH_2C_6H_3(NS)C_6H_3NH$ (hydrochloride: green needles), is obtained by oxidation of *p*-phenylenediamine (see above) and also of its leuco-base, the diaminophenothiazine (p. 279). It can also be prepared by nitration of phenothiazine, reduction to the leuco-base and subsequent oxidation; a method for detecting the presence of diphenylamine is based on this series of reactions. An isomer of thionine, **1-aminophenothiazine,** $C_6H_4(NS)C_6H_2(NH_2)NH$, is formed by oxidation of 1,3-diaminophenothiazine (p. 279) (*Kehrmann,* Ann. **322,** 57).

Methylene blue, $(CH_3)_2N\cdot C_6H_3(NS)C_6H_3N(CH_3)_2Cl$, *tetramethyldiaminophenazothionium chloride* (*Caro,* 1876), is prepared by oxidation of dimethyl-*p*-phenylenediamine in a solution containing H_2S, or of equimolecular proportions of dimethyl-*p*-phenylenediamine and dimethylaniline in the presence of thiosulfate. The reaction mechanism of these syntheses has been exhaustively studied. A similar course of reaction underlies the formation of all phenothiazime and phenothiazone dyes. According to the present generally accepted view, a preliminary formation of quinonediimines and indamines by dehydrogenation takes place; these, because of their known tendency to add amines and hydrogen sulfide, make possible the closure of the 1,4-thiazine ring. The formation of methylene blue can be divided into these steps:

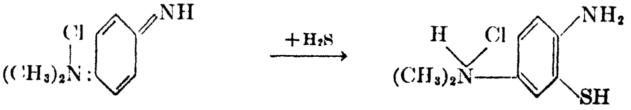
(*1*)

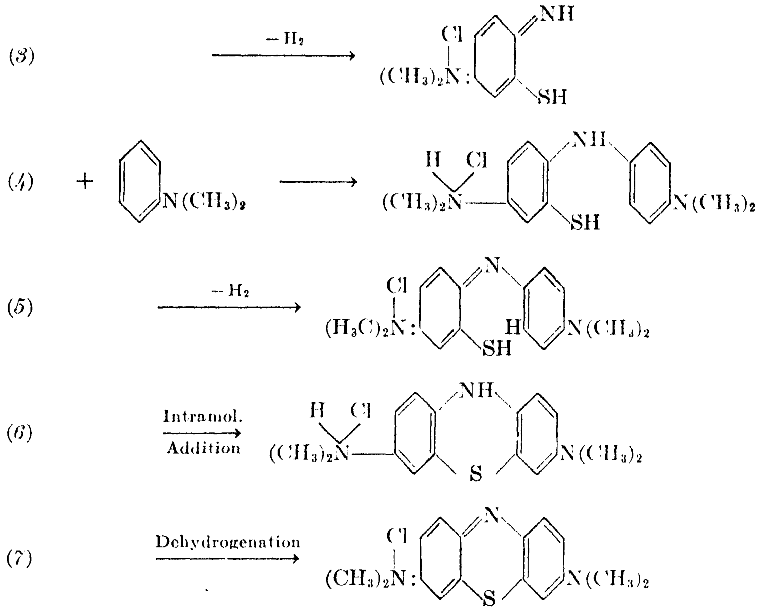


$$(CH_3)_2\overset{H\ Cl}{N}\cdot C_6H_4\cdot NH_2 \xrightarrow{-H_2} (CH_3)_2:\overset{Cl}{N}:C_6H_4:NH$$

Iminodimethylquinoniminium chloride

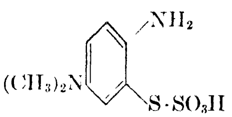
(*2*)





Methylene blue

When the synthesis starts with 2 molecules of dimethyl-*p*-phenylenediamine, the mechanism is the same except that ammonia is eliminated in step *3*. If the sulfur is introduced with sodium thiosulfate (according to *Bernthsen*), in step *2* 1-amino-4-dimethylaminobenzene-2-thiosulfonic acid is formed:



The sulfonic acid radical is removed by hydrolysis in subsequent steps.

Methylene blue (marketed as the hydrochloride or zinc chloride double salt) dyes silk or tannin-mordanted cotton a light-fast blue. Another important use is its application in microscopy to distinguish different cells in the tissues of living organisms (intra-vital staining, *Ehrlich*) (see *Ehrlich's* obituary, Ber. **49**, 1225). A silver compound of methylene blue is used under the name *argochrom* in septic diseases.

Methylene blue is converted by reduction ($Na_2S_2O_4$, alkaline solution) to ***leucomethylene blue*** (*3,7-dimethylaminophenothiazine*), m.p. 185°, yellow needles (*Cohn*, Ber. **33**, 1567; *Weil, Dürrschnabel, Landauer*, Ber. **44**, 3172; *Landauer, Weil*, Ber. **43**, 198). Methylene blue is not decolorized by formaldehyde alone, but if the reaction is carried out in the presence of unpasteurized milk, it is decolorized, since raw milk contains an enzyme (a dehydrogenase) which activates hydrogen, for which the methylene blue acts as acceptor. This decolorization, known as the *Schardinger* reaction, is used to distinguish between raw and pasteurized milk [*Schardinger*, Z.Untersuch.Nahr.u.Genuss. **5** (1902), 1113; *Wieland*, Ber. **45**, 2609; **55**, 3641; *Wieland, Rosenfeld*, Ann. **477**, 32].

Phenothiazone, $C_6H_4(SN)C_6H_3O$, m.p. 166°, red-brown flakes, is obtained from hydroxyphenothiazine by oxidation and from phenothiazime by digestion with soda solution. **5-Benzo[*a*]phenothiazone**, $C_6H_4(NS)C_{10}H_5O$, m.p. 176°, formed when benzo[*a*]phenazothionium sulfate is allowed to stand in aqueous solution (*Kehrmann, Christopoulos*, Ber. **54**, 651). **Dibenzophenothiazone**,

$C_{10}H_6(NS)C_{10}H_5O$, m.p. 245°, from phenyldibenzophenothiazime by treatment with dilute mineral acids (*Kehrmann*, Ann. **322**, 52).

7-**Hydroxyphenothiazone, thionol,** $HO{\cdot}C_6H_3(NS)C_6H_3O$, from thionine by digestion with dilute acids or alkalis and from hydroquinone and *p*-aminophenol by condensation with sulfur and subsequent oxidation. Hydroquinone, *p*-phenylenediamine, and sulfur give thionoline, $NH_2C_6H_3(NS)C_6H_3{:}O$ (Ger. Pat. 103301, 1897).

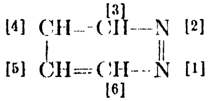
The blue and black substantive cotton dyes produced by the fusion of *p*-amino- and *p*-nitrophenols, nitro- and nitrohydroxydiphenylamines and indophenols with sulfur at temperatures between 140° and 200°, which are known as **sulfur dyes,*** are at least in part 1,4-thiazine derivatives. They are amorphous substances with high molecular weights, insoluble in acids and alkalis. When treated with sodium sulfide they dissolve even in the cold, and are precipitated unchanged from this solution by the action of air; this behavior permits their use with vat-dyeing techniques. The dull dyeings produced with them are characterized by great fastness to light and washing, which can be increased by aftertreatment with metal salts (chromium, copper). The constitution of many sulfur dyes is not known with certainty. They are di- and polysulfides of thiazines (*cf. v. Weinberg*, Ber. **A63**, 121), which are converted by sodium sulfide to mercaptothiazines, which are soluble in alkali and easily oxidized. The presence of the thiazine ring in these dyes has been proved for one of them, immedial pure blue (see below), by conversion to tetrabromodimethylaminophenothiazone (*Gnehm, Kaufler*, Ber. **37**, 2617, 3032; *cf. Gnehm, Kaufler*, Ber. **39**, 1016; Ger. Pat. 140964, 1902, Frdl. **VII**, 522; Ger. Pat. 178940, 1905, Frdl. **VIII**, 755).

The first technically important sulfur dye, now obsolete, was Vidal Black, from *p*-aminophenol or *p*-aminocresol (*Vidal*, Mon. sci. [4] **11**, II, 655; C. **1897, II**, 747; Ger. Pat. 99040, 1897). Among the sulfur dyes which have been prepared, these are outstanding: sulfur black (from 2,4-dinitrophenol), immedial black (from 2,4-dinitro-4′-hydroxydiphenylamine) and immedial pure blue (from 4-hydroxy-4′-dimethylaminodiphenylamine).

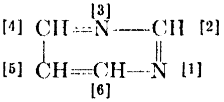
Another group of yellow and brown dyes, obtained by fusing *m*-toluenediamine and related compounds with sulfur and alkali sulfides, are probably derived from the benzothiazoles (p. 143).

The selenium compound corresponding to phenothiazine, **phenoselenazine** (*Cornelius*, J.pr. **88**, 395), and a series of analogous dyes (*Abderhalden, Fodor*, Ber. **49**, 577; *Karrer*, Ber. **51**, 190) have been prepared.

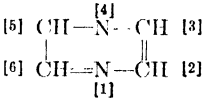
3. DIAZINES



Pyridazine, 1,2-Diazine,
o-Diazine



Pyrimidine, 1,3-Diazine,
m-Diazine



Pyrazine, 1,4-Diazine,
p-Diazine

The trivial names are a combination of pyridine and the symbol az- or imid-. The diazine formulas may be derived from the pyridine formula by replacement of successive methine groups by nitrogen atoms (*cf.* the introduction, page 6).

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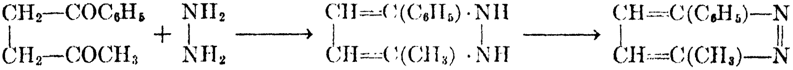
* *Cain* and *Thorpe:* Synthetic Dyestuffs and Intermediate Products (Griffin, London, 1933). *Bucherer:* Lehrbuch der Farbenchemie (Spamer, Leipzig, 1921). *Fierz-David* and *Blagney:* Grundlegende Operationen der Farbenchemie (Springer Berlin, 1938). *v. Georgievics:* Kurzes Lehrbuch der Farbenchemie (1921). Patents in Friedländer, Teerfarben, Vol. V to XX. *v. Weinberg:* Ber. **63**, Abt. A, 117 (1930). *Schultz:* Farbstofftabellen (Weidmann, Berlin, 1923). *Rowe:* Colour Index (London, 1924).

(a) Pyridazines (1,2-Diazines)

(1) **PYRIDAZINES** or 1,2-**DIAZINES** are prepared by the following methods:

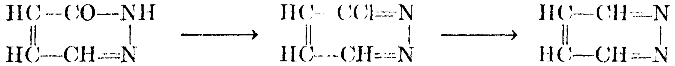
1. 1,4-Diketones and hydrazine hydrate give dihydropyridazines, which are partly oxidized even by air or autoxidation to pyridazines (*Paal, Dencks*, Ber. **36,** 491):



$$\begin{array}{l}CH_2-COC_6H_5\\ |\\ CH_2-COCH_3\end{array} + \begin{array}{l}NH_2\\ |\\ NH_2\end{array} \longrightarrow \begin{array}{l}CH{=}C(C_6H_5)\cdot NH\\ | \qquad\qquad\qquad |\\ CH{=}C(CH_3)\cdot NH\end{array} \longrightarrow \begin{array}{l}CH{=}C(C_6H_5)-N\\ | \qquad\qquad\qquad \|\\ CH{=}C(CH_3)-N\end{array}$$

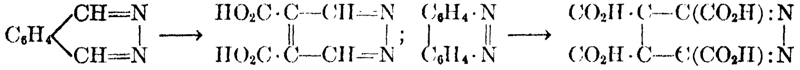
For the mechanism of this reaction, see *Korschun, Roll*, Bull. [4] **39,** 1223.

2. Pyridazones (p. 284) are converted by $POCl_3$ to chloropyridazines, which yield pyridazines when reduced with hydriodic acid and phosphorus (*Oppenheim*, Ber. **34,** 4227):

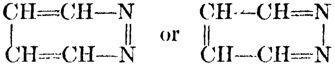


$$\begin{array}{l}HC-CO-NH\\ \| \qquad\quad |\\ HC-CH{=}N\end{array} \longrightarrow \begin{array}{l}HC-CCl{=}N\\ \| \qquad\quad |\\ HC-CH{=}N\end{array} \longrightarrow \begin{array}{l}HC-CH{=}N\\ \| \qquad\quad |\\ HC-CH{=}N\end{array}$$

3. Phthalazines and benzo[*c*]cinnolines (pp. 285, 287), the benzo and dibenzo derivatives of pyridazine, are oxidized to pyridazinecarboxylic acids by permanganate (*Gabriel*, Ber. **36,** 3373):



$$C_6H_4\begin{array}{l}\diagup CH{=}N\\ \qquad\quad |\\ \diagdown CH{=}N\end{array} \longrightarrow \begin{array}{l}HO_2C\cdot C-CH{=}N\\ \qquad\quad \| \qquad |\\ HO_2C\cdot C-CH{=}N\end{array};\ \begin{array}{l}C_6H_4\cdot N\\ | \qquad\ \|\\ C_6H_4\cdot N\end{array} \longrightarrow \begin{array}{l}CO_2H\cdot C-C(CO_2H):N\\ \qquad\quad | \qquad\qquad |\\ CO_2H\cdot C-C(CO_2H):N\end{array}$$

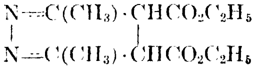
PYRIDAZINE, 1,2-*diazine*,  $\begin{array}{l}CH{=}CH-N\\ | \qquad\quad \|\\ CH{=}CH-N\end{array}$ or $\begin{array}{l}CH-CH{=}N\\ \| \qquad\quad |\\ CH-CH{=}N\end{array}$, m.p. −8°, b.p. 205°, is obtained: (*1*) from nitrosuccinaldehyde, or the fumardialdehyde formed from it, with hydrazine hydrate (*Marquis*, C.r. **136,** 368); (*2*) from pyridazine-3-carboxylic acid or (*3*) pyridazinetetracarboxylic acid by decarboxylation; (*4*) from pyridazone by method *2* (*Gabriel*, Ber. **42,** 654). Pyridazine smells like pyridine, forms soluble salts with acids and combines with $AuCl_3$, $HgCl_2$, and the like.

3-**Methyl-,** 3-**phenyl-** and 3-**phenyl-**5-**methylpyridazine,** b.p. 214°, m.p. 103° (b.p. 332°) and m.p. 95°, were prepared from the corresponding pyridazones by method *2* (see above). 3-**Methyl-**6-**phenylpyridazine,** m.p. 103°; 3,6-**diphenylpyridazine,** m.p. 222°; 3,4,6-**triphenylpyridazine,** m.p. 171°, from 1,4-diketones according to method *1* (see above). 3,6-**Dimethylpyridazine,** m.p. 32°, b.p. 215°, very hygroscopic, is obtained from its dicarboxylic acid (*Wohlgemuth*, Ber. **37,** 4362). 3-Methylpyridazine condenses like quinaldine (p. 232) with benzaldehyde and phthalic anhydride.

3-**Pyridazinecarboxylic acid** is formed by oxidation of 3-(hydroxyphenyl)-pyridazine, prepared according to Method *2* (see above), with permanganate (*Gabriel, Colman*, Ber. **32,** 395). 6-**Phenylpyridazine**-3-**carboxylic acid,** m.p. 131°, from 3-methyl-6-phenylpyridazine with dilute nitric acid (*Paal, Dencks*, Ber. **36,** 491). 3,6-**Dimethylpyridazine**-4,5-**dicarboxylic acid ester,** m.p. 56°, from its dihydro derivative (see below) with nitrous acid. **Pyridazine**-4,5-**dicarboxylic acid,** m.p. 213° (dec.), from phthalazine, and **pyridazinetetracarboxylic acid** from benzo[*c*]cinnoline (see above). 4-**Phenylpyridazine**-5,6-**dicarboxylic acid,** 4-*phenylcinnolinic acid*, m.p. 221°, from 4-phenylcinnoline (p. 285).

DIHYDROPYRIDAZINES are obtained from 1,4-diketones and hydrazines partly or wholly in place of the expected N-aminopyrroles (*cf.* method *1*, above). 1-**Phenyl**-3-**methyl**-1,2-**dihydropyridazine,** m.p. 197° (dec.), from levulinaldehyde and phenylhydrazine (*Harries*, Ber. **31,** 45). 3,4,6-**Triphenyldihydropyridazine,** m.p. 187°, from desylacetophenone with hydrazine, yields the corresponding phenazine when it is treated with chromic acid. 1,3,4,6-**Tetraphenyldihydropyridazine,** $C_4H_2(C_6H_5)_4N_2$, m.p. 149°, from desylacetophenone with phenylhydrazine, is converted by dry distillation to 1,3,4-triphenylpyrazole

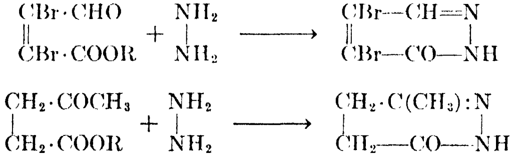
(p. 95) (*Smith*, Ann. **289**, 310). **3,6-Dimethyldihydropyridazine-4,5-dicarboxylic acid ester:**



$$\begin{array}{l} N{=}C(CH_3)\cdot CHCO_2C_2H_5 \\ |\qquad\qquad\quad\;\; | \\ N{=}C(CH_3)\cdot CHCO_2C_2H_5 \end{array}$$

is formed from α,β-diacetylsuccinic acid and hydrazine hydrate in alcoholic solution, and reacts with another mol of hydrazine to give the cyclic hydrazide of the acid (*Paal, Ubber*, Ber. **36**, 497; *Bülow*, Ber. **37**, 91).

OXODIHYDROPYRIDAZINES, or **PYRIDAZONES**, and **OXOTETRAHYDROPYRIDAZINES**, or **DIHYDROPYRIDAZONES**, result from the reaction of 1,4-oxocarboxylic acid esters with hydrazine hydrate or monosubstituted hydrazines; they may be considered to be ring-homologues of pyrazolone (p. 103):



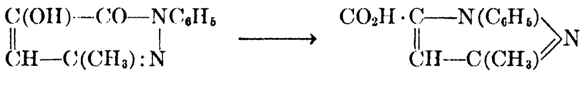
$$\begin{array}{l} CBr\cdot CHO \\ \| \\ CBr\cdot COOR \end{array} + \begin{array}{l} NH_2 \\ | \\ NH_2 \end{array} \longrightarrow \begin{array}{l} CBr{-}CH{=}N \\ \|\qquad\quad\;\; | \\ CBr{-}CO{-}NH \end{array}$$

$$\begin{array}{l} CH_2\cdot COCH_3 \\ | \\ CH_2\cdot COOR \end{array} + \begin{array}{l} NH_2 \\ | \\ NH_2 \end{array} \longrightarrow \begin{array}{l} CH_2\cdot C(CH_3){:}N \\ |\qquad\qquad\quad\; | \\ CH_2{-}CO{-}NH \end{array}$$

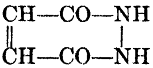
The dihydropyridazones are readily oxidized to pyridazones. The pyridazones are converted by $POCl_3$ to chloropyridazines (p. 283), in which the chlorine atom is easily replaced by hydrogen or other substituents.

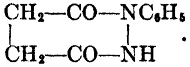
PYRIDAZONES. 3(2)-**Pyridazone**, $C_4H_4ON_2$, m.p. 104°, is obtained from its carboxylic acid, which is the product of the oxidation of oxotetrahydropyridazine-3-carboxylic acid with bromine (*Gabriel*, Ber. **42**, 657). **Dibromopyridazone**, m.p. 224°, from mucobromic acid with hydrazine (see above). 3-**Methylpyridazone**, m.p. 143°. 3-**Phenylpyridazone**, m.p. 202°; 5-**methyl**-3-**phenylpyridazone**, m.p. 190°; 1-**phenyl**-3-**methylpyridazone**, m.p. 82°, from the corresponding dihydropyridazones with bromine (*Oppenheim*, Ber. **34**, 4227, and others).

DIHYDROPYRIDAZONES, PYRIDAZINONES. 4,5-**Dihydro**-3(2)-**pyridazone, pyridazinone**, $C_4H_6ON_2$, b.p. 170°, is formed by the decarboxylation of 3-**oxo**-2,3,4,5-**tetrahydropyridazine**-6-**carboxylic acid**, $C_4H_5ON_2COOH$, m.p. 198°, the product of the condensation of α-oxoglutaric acid with hydrazine (*Gabriel*, Ber. **42**, 655); it decomposes when digested with alkalis, splitting into hydrazine and other products. 6-**Methyl**-4,5-**dihydro**-3(2)-**pyridazone**, m.p. 94°, and the 6-**phenyl** derivative, m.p. 149°, are obtained from levulinic acid ester and β-benzoylpropionic acid ester. 6-**Phenyl**-3-**oxo**-2,3,4,5-**tetrahydropyridazine**-4-**carboxylic acid ester**, m.p. 156°, from benzoylmethylmalonic acid with hydrazine hydrate. 4-**Methyl**-6-**phenyl**-4,5-**dihydro**-3(2)-**pyridazone**, m.p. 157°, from benzoylisobutyric acid with hydrazine (*Oppenheim*, Ber. **34**, 4230). 2-**Phenyl**-6-**methyl**-4,5-**dihydro**-3(2)-**pyridazone**, $C_4H_4(CH_3)ON_2C_6H_5$, m.p. 107°, b.p. 340–350°, is converted by PCl_5 and glacial acetic acid into 2-phenyl-6-methyl-3(2)-pyridazone (see above), and phenylmethylchloropyridazone, which gives phenylmethylethoxypyridazone with sodium ethylate. Saponification of the latter yields phenylmethylhydroxypyridazone, which rearranges when heated with HCl at 170° to 1-phenyl-3-methylpyrazole-5-carboxylic acid (p. 100):

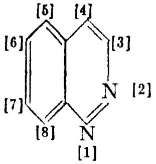


$$\begin{array}{l} C(OH){-}CO{-}NC_6H_5 \\ \|\qquad\qquad\quad\;\; | \\ CH{-}C(CH_3){:}N \end{array} \longrightarrow \begin{array}{l} CO_2H\cdot C{-}N(C_6H_5) \\ \qquad\quad\;\, \| \\ \qquad\quad CH{-}C(CH_3) \end{array}\!\!{>}N$$

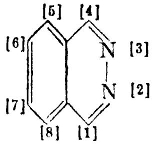
Maleic acid hydrazide,  $\begin{array}{l} CH{-}CO{-}NH \\ \|\qquad\qquad\; | \\ CH{-}CO{-}NH \end{array}$, m.p. over 250°, is a dioxotetrahydropyridazine. It is formed together with the isomeric N-aminomaleimide from maleic anhydride and hydrazine (*Foesterling*, J.pr. **51**, 371). The cyclic hydrazides of the succinic acid series, formed by heating the acid chlorides with hydrazine hydrochlorides (Vol. III, p. 160), are dioxohexahydropyridazines, or *ortho*-

piperazones. **1-Phenyl-1,2-dihydro-3,6-pyridazinedione**:  $\begin{array}{l}CH_2—CO—NC_6H_5\\ | \qquad\qquad\quad |\\ CH_2—CO—NH\end{array}$.

(2) **BENZOPYRIDAZINES.** There are two isomeric benzopyridazines, one having the benzo ring attached to the 3- and 4-C-atoms of the pyridazine ring, and the other having it attached to the 4- and 5-C-atoms. The former is **cinnoline,** and the latter, **phthalazine:**

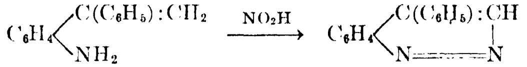


Cinnoline
Benzo[*c*]pyridazine

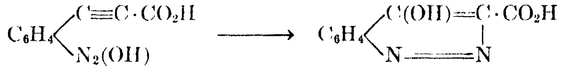


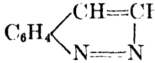
Phthalazine
Benzo[*d*]pyridazine

Cinnolines are formed by the action of nitrous acid on *o*-aminostyrenes (*Widman*, Ber. **17**, 722; *Stoermer, Fincke*, Ber. **42**, 3115):

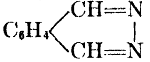

$$C_6H_4\left\langle\begin{array}{l}C(C_6H_5):CH_2\\ NH_2\end{array}\right. \xrightarrow{NO_2H} C_6H_4\left\langle\begin{array}{l}C(C_6H_5):CH\\ \qquad\qquad\quad |\\ N\!=\!=\!=\!=\!=\!N\end{array}\right.$$

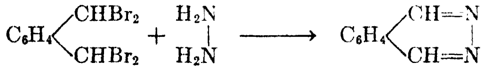
Hydroxycinnolinecarboxylic acid is obtained from *o*-(carboxyethynyl)-benzenediazonium chloride by warming with water:


$$C_6H_4\left\langle\begin{array}{l}C\equiv C\cdot CO_2H\\ N_2(OH)\end{array}\right. \longrightarrow C_6H_4\left\langle\begin{array}{l}C(OH)=C\cdot CO_2H\\ \qquad\qquad\quad |\\ N\!=\!=\!=\!=\!=\!N\end{array}\right.$$

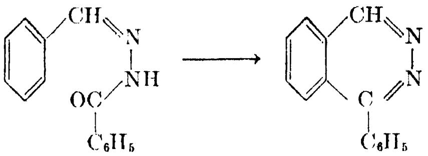
Cinnoline,  $C_6H_4\left\langle\begin{array}{l}CH=CH\\ \qquad\ |\\ N\!=\!=\!N\end{array}\right.$, m.p. 39°, strongly basic, poisonous, soluble in water and organic solvents, is prepared from 4-**hydroxycinnoline-3-carboxylic acid,** m.p. 260° (see above). The acid can be decarboxylated to 4-**cinnolinol,** $C_8H_5N_2(OH)$, m.p. 225°; the latter reacts with PCl_5 to give 4-**chlorocinnoline,** $C_8H_5N_2Cl$, whose chlorine atom can be easily displaced by groups such as OH, OC_2H_5, and NHC_6H_5. Reduction of 4-chlorocinnoline with iron filings and sulfuric acid yields **dihydrocinnoline,** $C_6H_4(C_2H_4N_2)$, m.p. 88°, which can be oxidized to cinnoline with HgO (*Busch, Klett*, Ber. **25**, 2847; *Busch, Rast*, Ber. **30**, 521).

4-**Phenylcinnoline** (see above), sulfur-yellow crystals, m.p. 67°, is obtained from *o*-amino-1,1-diphenylethylene with nitrous acid; it is oxidized by $KMnO_4$ to 4-phenylpyridazine-5,6-dicarboxylic acid (p. 283) (*Borsche*, Ber. **42**, 1315). 4-**Methylcinnolinecarboxylic acid,** $COOHC_6H_3[C_2NH_2(CH_3)]$, yellow crystals, m.p. 230°, from *o*-aminopropenylbenzoic acid (*Widman*, Ber. **17**, 722).

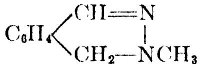
PHTHALAZINE,  $C_6H_4\left\langle\begin{array}{l}CH=N\\ \qquad\ |\\ CH=N\end{array}\right.$, m.p. 91°, b.p. 189° (29 mm.), hydrochloride, m.p. 231°, is prepared from $\alpha,\alpha,\alpha',\alpha'$-tetrachloro- or, better, tetrabromo-*o*-xylene with hydrazine solution:


$$C_6H_4\left\langle\begin{array}{l}CHBr_2\\ CHBr_2\end{array}\right. + \begin{array}{l}H_2N\\ \ \ |\\ H_2N\end{array} \longrightarrow C_6H_4\left\langle\begin{array}{l}CH=N\\ \qquad\ |\\ CH=N\end{array}\right.$$

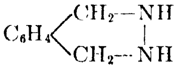
and also from chlorophthalazine by reduction with hydriodic acid and phosphorus (*Gabriel, Eschenbach*, Ber. **30**, 3024; *Gabriel*, Ber. **36**, 3377). A general synthesis for 1-substituted phthalazines, analogous to the method of forming the isoquinoline ring, consists in the treatment of the benzoylhydrazones of benzaldehydes with hydrochloric acid in amyl alcohol solution (*Aggarwal, Darbari, Ray*, J. **1929**, 1941):



With methyl iodide phthalazine forms an addition product, $C_8H_6N_2 \cdot ICH_3$; the latter reacts with silver oxide to form 2-methyl-1(2)-phthalazone (p. 287) and with aqueous potassium hydroxide to give the same methylphthalazone, and also **2-methyl-1,2-dihydrophthalazine** (I), which oxidizes rapidly in the air to the methylphthalazone (*cf.* the similar reaction of the alkylquinolinium iodides, p. 230). Phthalazine is reduced by sodium amalgam to 1,2,3,4-**tetrahydrophthalazine** (II), and by zinc dust and hydrochloric acid to α,α'-diaminoxylene,

(I) 

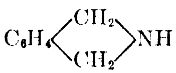
$$C_6H_4\left\langle\begin{matrix}CH{=}N\\ \quad|\\ CH_2{-}NCH_3\end{matrix}\right.$$

 (II)

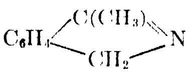
$$C_6H_4\left\langle\begin{matrix}CH_2{-}NH\\ \quad|\\ CH_2{-}NH\end{matrix}\right.$$

$C_6H_4(CH_2NH_2)_2$ (Vol. III, p. 107) (*Gabriel, Pinkus*, Ber. **26**, 2210; *Gabriel, Müller*, Ber. **28**, 1830). Alkaline permanganate solution oxidizes phthalazine to 4,5-pyridazinedicarboxylic acid (*Gabriel*, Ber. **36**, 3378).

Chlorophthalazine, $C_6H_4(C_2HClN_2)$, m.p. 113°, and also 1-**methyl-**, 1-**propyl-**, and 1-**isobutylchlorophthalazine**, m.p. 130°, 67°, and an oil, are obtained from phthalazone and alkylated phthalazones with $POCl_3$. 1,4-**Dichlorophthalazine**, m.p. 165°, by the action of $POCl_3$ on phthalylhydrazine (Vol. III, p. 387) (Ger. Pat. 481650, 1925, Frdl. **XVI**, 541). When reduced these chloro compounds form derivatives of isoindole; chlorophthalazine yields 1,3-*dihydroisoindole* (III) (for derivatives, see *Fränkel*, Ber. **33**, 2810; *v. Braun*, Ber. **43**, 1353) and 1-methylchlorophthalazine gives 1-*methylisoindole* (IV), which can be reduced to *methyldihydroisoindole*. The other homologues behave similarly (*Bromberg*, Ber. **29**, 1434). With phosphorus and hydriodic acid the reduction of the chlorophthalazines can be stopped at the phthalazine stage (*Gabriel, Eschenbach*, Ber. **30**, 3022; *Paul*, Ber. **32**, 2014).

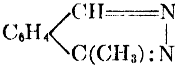
(III) 

$$C_6H_4\left\langle\begin{matrix}CH_2\\ \\ CH_2\end{matrix}\right\rangle NH$$

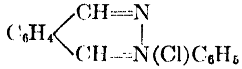
 (IV)

$$C_6H_4\left\langle\begin{matrix}C(CH_3)\\ \\ CH_2\end{matrix}\right\rangle N$$

1-**Methylphthalazine** (V), m.p. 74°, condenses like quinaldine (p. 232) with phthalic anhydride, chloral, and benzaldehyde to form $(C_8H_5N_2)CH{:}C_2O_2C_6H_4$, $(C_8H_5N_2)CH_2 \cdot CH(OH)CCl_3$, and $(C_8H_5N_2)CH{:}CHC_6H_5$, respectively (*Gabriel, Eschenbach*, Ber. **30**, 3033). 1-**Ethylphthalazine**, $C_8H_5N_2(C_2H_5)$, m.p. 23°, b.p. 190° (16 mm.), from ethylchlorophthalazine.

(V) 

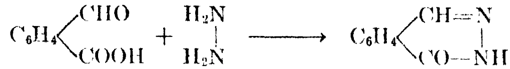
$$C_6H_4\left\langle\begin{matrix}CH{=}N\\ \qquad|\\ C(CH_3){:}N\end{matrix}\right.$$

 (VI)

$$C_6H_4\left\langle\begin{matrix}CH{=}N\\ \quad|\\ CH{=}N(Cl)C_6H_5\end{matrix}\right.$$

1-**Phenyl-** and 1-**benzylphthalazine**, m.p. 142° and 82°, from the corresponding phthalazones (*Loeck*, Ber. **38**, 3918). 2-**Phenylphthalazinium chloride** (VI), m.p. 107°, is formed by the condensation of *o*-phthalaldehyde with phenylhydrazine hydrochloride; with alkalis it gives 2-phenyldihydro-1-phthalazinol, m.p. 129°, which with hydrochloric acid regenerates the phenylphthalazinium chloride (*Thiele, Falk*, Ann. **347**, 114).

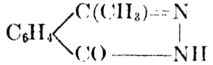
PHTHALAZONES, oxodihydrophthalazines, are obtained from aromatic *o*-formyl- and *o*-oxocarboxylic acids with hydrazines:

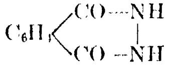


Phthalaldehydic acid 1(2)-Phthalazone

PHTHALAZONE, m.p. 183°, b.p. 337°, can be prepared from oxodihydrophthalazinecarboxylic acid, the condensation product of phthalonic acid with hydrazine (*Fränkel*, Ber. **33**, 2808), or directly from phthalaldehydic acid and hydrazine (*Seekles*, Rec. **43**, 329). Phthalazone forms a potassium salt, $C_8H_5ON_2K$, when treated with alcoholic KOH, N-acetylphthalazone with acetyl chloride and N-methylphthalazone with methyl iodide. The latter compound is also obtained from N-methylphthalazinium iodide (p. 286).

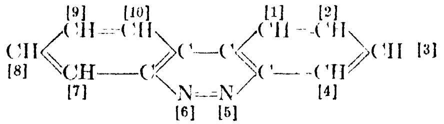
4-Methyl-1(2)-phthalazone (I), m.p. 220°, b.p. 348°, from *o*-acetylbenzoic acid (*Gabriel, Neumann*, Ber. **26**, 524; *Liebermann, Bistrzyski*, Ber. **26**, 535). **4-Ethyl-, propyl-, isobutyl-,** and **benzyl-1(2)-phthalazone**, m.p. 169°, 156°, 113°, and 152° (*Bromberg*, Ber. **29**, 1434; *Paul*, Ber. **32**, 2016). **4-Phenyl-1(2)-phthalazone**, m.p. 106°, from phthalaldehydic acid and phenylhydrazine (*Seekles*, Rec. **43**, 329).

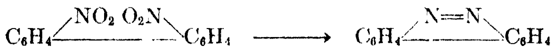
(I) 

 (II)

Phthalazinediones are the cyclic hydrazides of phthalic acids. Since they correspond to the *o*-piperazones (p. 285), they are also known as benzo-*o*-piperazones. **1,4-Phthalazinedione**, *phthaloylhydrazine* (II), m.p. over 250°, is formed from phthalic acid ester, chloride, or anhydride with hydrazine (*Radenhausen*, J.pr. **52**, 447; *Davidis*, J.pr. **54**, 66); with $POCl_3$ it gives 1,4-dichlorophthalazine (Ger. Pat. 481650, 1925). **2-Phenyl-1,4-phthalazinedione**, *phthaloylphenylhydrazine*, from phthalic acid monophenylhydrazide by heating.

Benzo[*c*]cinnoline, phenazone,* dibenzopyridazine, crystallizes in the form of yellow needles, m.p. 156°, is isomeric with phenazine (p. 305). It is prepared from 2,2′-dinitrodiphenyl by electrolytic reduction or by reduction with sodium amalgam and methanol; an intramolecular formation of an azo group takes place:





The monoxide and dioxide of benzo[*c*]cinnoline are formed as intermediate products. Benzocinnoline oxide (m.p. 139°) is also quickly obtained by reduction of 2,2′-dinitrodiphenyl with sodium sulfide; it is reduced to benzocinnoline by stannous chloride (*Ullmann, Dieterle*, Ber. **37**, 24). Another method for preparing benzo[*c*]cinnoline is to heat 2,2′-dihydrazinodiphenyl with hydrochloric acid at 150°. Reduction of benzocinnoline with tin and HCl gives **5,6-dihydrobenzo[*c*]cinnoline**, $C_{12}H_8(N_2H_2)$ (*Täuber*, Ber. **24**, 3083). Benzocinnoline is a base; it adds alkyl iodides (*Ullmann, Dieterle*, Ber. **37**, 25). The relation of benzo[*c*]cinnoline to pyridazine is evident from its oxidation by permanganate to pyridazinetetracarboxylic acid (p. 283).

Dimethylbenzo[*c*]cinnoline, *tolazone*, $(C_7H_6)_2N_2$, m.p. 187°, is obtained from 2,2′-dinitrodimethyldiphenyl (*Meyer*, Ber. **26**, 2239). **2,9-Dimethylbenzo[*c*]-cinnoline**, m.p. 188°; **2,9-diaminobenzo[*c*]cinnoline**, m.p. 265° (*Ullmann, Dieterle*, Ber. **37**, 23).

Compounds containing a pyridazine ring combined with a triazole ring have been prepared by condensation of N-aminotriazole with 1,3-diketones and *β*-oxocarboxylic acids esters (*cf*. p. 156, and *Bülow*, Ber. **42**, 2594).

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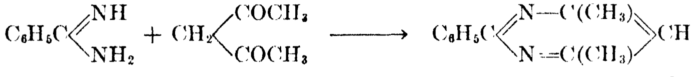
* Antipyrine (p. 106) is also sometimes called phenazone.

(b) 1,3-Diazines

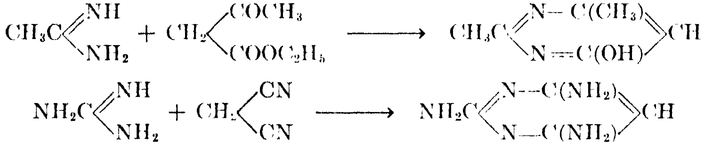
(1) **PYRIMIDINES.** Pyrimidines, or 1,3-diazines, are ring-homologues of the imidazoles (p. 124), and, like them, may be regarded as cyclic amidines. Purines, containing a pyrimidine ring fused to an imidazole ring, are mostly treated in Vol. I, because of their relation to uric acid and the ureides of the malonic acid series.

Pyrimidines are prepared by the following methods:

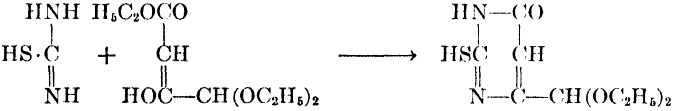
1. From carboxylic acid amidines with 1,3-diketones (*Pinner*, Ber. **26**, 2125):



The reaction of amidines with β-formyl- and β-oxocarboxylic acids gives hydroxypyrimidines, and with cyanoacetic ester, aminohydroxypyrimidines. If ureas, thioureas, or guanidines are used in place of amidines, dihydroxypyrimidines (uracils), aminohydroxy- and diaminohydroxypyrimidines, respectively, are produced. These compounds have been partially described in Vol. I, in connection with the purine group.

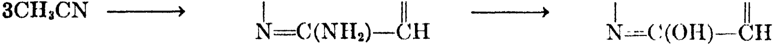


The synthesis with thioureas, in particular, can be varied widely. For example, with γ-diethoxyacetoacetic ester, a formyl group is introduced in the 4-position; this is the only reaction now known that yields aldehydes of the pyrimidine series [*Johnson, Cretcher*, Am. **37**, 2144; J.Biol.Chem. **26** (1917), 99]:

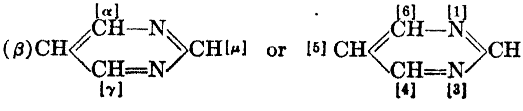


With $POCl_3$ the hydroxypyrimidines give chloropyrimidines, which are generally converted to pyrimidines by digestion with zinc dust and water.

2. Aminopyrimidines (cyanoalkines) are formed when nitriles of fatty acids are heated with sodium or sodium alcoholate at 150°. The structure of the aminopyrimidines is evident from their conversion by nitrous acid to the hydroxypyrimidines obtained according to method *1* [*Holtzwart*, J.pr. **39**, 230; *v. Meyer*, Ber.Verhandl.K.sächs.Ges.Wiss. **57** (1906), 324]:



The intermediate products of this reaction are probably imines of β-oxocarboxylic acid nitriles, such as $CH_3C(:NH)CH_2CN$, (*cf.* Vol. I), which combine with a third molecule of the nitrile to give aminopyrimidines. Mixtures of two alkyl cyanides also give aminopyrimidines when heated with sodium or sodium alcoholate.

PYRIMIDINE, , m.p.

21°, b.p. 124° (760 mm.), a base of narcotic odor, soluble in water, precipitated by sublimate. It is prepared by dry distillation of 4-pyrimidinecarboxylic acid or by digestion of tri- or tetrachloropyrimidine with zinc dust and water (*Bülow*, *Schlesinger*, Ber. **33**, 3366; *Emery*, Ber. **34**, 4178). It forms a characteristic molecular compound with $HgCl_2$, which is sparingly soluble in water. Gold chloride compound, m.p. 226°; picrate, m.p. 156°.

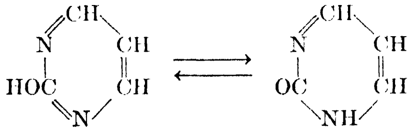
The following derivatives were prepared in the usual way, that is, by reduction of chlorinated pyrimidines. 4-**Methylpyrimidine**, m.p. 142°; 5-**methylp.**, m.p. 30°, b.p. 152°; 2-**methylp.**, m.p. −5°, b.p. 138°; 4,5-**dimethylp.**, m.p. 3°, b.p. 177°; 4,6-**dimethylp.**, m.p. 25°; b.p. 159°; 2,4-**dimethylp.**, b.p. 146°; 4-**methyl-5-ethylp.**, b.p. 193°; 4-**methyl-2-phenylp.**, m.p. 22°, b.p. 270°; 2,4-**diethyl-5-methylp.**, *cyanoconiine*, b.p. 205°, having an action similar to coniine (p. 332) (*Gerngross*, Ber. **38**, 3394). 4,6-**Dimethyl-2-phenylp.**, m.p. 83°, b.p. 276°, from benzamidine and acetylacetone (see above).

The methyl group between the two N-atoms, as in the case of picoline and quinaldine, condenses with benzaldehyde to $P\cdot[4]CH:CHC_6H_5$, $P\cdot[6](CH:CHC_6H_5)_2$, *etc.* (*Gabriel*, *Colman*, Ber. **36**, 3383). 4-Methylpyrimidine, prepared very easily from methyluracil (see below), decomposes to 1,3-diaminobutane when reduced with Na and alcohol (*Byk*, Ber. **36**, 1924; *Johnson*, *Joyce*, Am. **38**, 1854).

No simple preparation for *pyrimidinecarboxaldehydes* is known. By circuitous methods a few hydroxy- and dihydroxypyrimidinecarboxaldehydes have been obtained (see p. 291).

CARBOXYLIC ACIDS are formed by oxidation of methylpyrimidines with $KMnO_4$. Carboxyl groups next to N-atoms are easily removed. 4-**Pyrimidinecarboxylic acid**, m.p. 240° (dec.), from 4-methylpyrimidine. 5-**Methylp.-4-carboxylic acid**, from 4,5-dimethylp. (*Schlenker*, Ber. **34**, 2825). 6-**Methylp.-4-carboxylic acid**, from 4,6-dimethylp., together with 4,6-pyrimidinedicarboxylic acid (*Angerstein*, Ber. **34**, 3956). 4,5-**Pyrimidinedicarboxylic** acid is obtained from quinazoline (benzopyrimidine, p. 292) by oxidation with $KMnO_4$; when heated it loses CO_2, leaving 5-pyrimidinecarboxylic acid (*Gabriel*, *Colman*, Ber. **37**, 3647).

HYDROXYPYRIMIDINES are tautomeric with pyrimidones (oxodihydropyrimidines):



The pyrimidone derivatives include many physiologically important compounds, which occur either as decomposition products of purines (such as uric acid) or as cleavage products of nucleic acids (Vol. I, p. 748). *Uracil* was first obtained by the hydrolysis of nucleic acid from yeast (*Ascoli*, Z.physiol.Chem. **31**, 162). *Thymine* and *cytosine* can be similarly isolated from the thymus nucleic acid (*Kossel*, *Neumann*, Ber. **26**, 2753; **27**, 2219).

The basic syntheses of pyrimidols are given on p. 288.

PYRIMIDOLS, MONOHYDROXYPYRIMIDINES. 2-**Pyrimidol**, 2(1)-**pyrimidone,** m.p. over 320°, from 2-ethylmercaptopyrimidine by acid hydrolysis (*Johnson*, *Joyce*, Am. **37**, 2151). 4-**Pyrimidol**, 4(3)-*pyrimidone*, m.p. 165°, from 2,4-dichloropyrimidine with concd. HI and red phosphorus [*Wheeler*, J.Biol. Chem. **3** (1907), 285]. 2-**Methyl-4-pyrimidol**, m.p. 212°, from acetamidine and malonaldehydic acid ester (*Gabriel*, Ber. **37**, 3639). 2-**Phenyl-4-pyrimidol**, m.p. 208°, b.p. 260–263° (30 mm.), from its carboxylic acid, whose ester, m.p. 214°, is obtained from benzamidine or benzamidoxime with dicarboxyglutaconic acid ester (*Ruhemann*, *Hemmy*, Ber. **30**, 1488; *Wolf*, Ber. **30**, 1564). 2,4-**Dimethyl-6-pyrimidol**, m.p. 192°, from acetoacetic ester and acetamidine, or from 2,4-dimethyl-6-aminopyrimidine (see below) with nitrous acid. 4,6-**Dimethyl-2-pyrimidol**, m.p. 198°, from acetylacetone and urea (*Angerstein*, Ber. **34**, 3956; *Stark*, *Bögemann*, Ber. **43**, 1126). 2-**Phenyl-4-methyl-6-pyrimidol**, m.p. 216° (*Schmidt*, Ber. **35**, 1575).

PYRIMIDINEDIOLS (*dihydroxypyrimidines*) or uracils are obtained from β-oxocarboxylic acid esters and urea, from aminopyrimidols with HNO_3 or by heating with hydrochloric acid or from hydrouracils with bromine.

URACIL = 2,4(1,3)-**pyrimidinedione** or 2,4-**pyrimidinediol** (synthesis, properties, Vol. I, p. 628). **Thymine** (5-*methyluracil*) and 4-**methyluracil** (Vol. I, pp. 628–629). 4,5-**Dimethyluracil**, m.p. 290°; 4-**methyl**-5-**ethyluracil** (*Byk*, Ber. **36**, 1915), etc.

2,4,6-Pyrimidinetriol, 2,4,6(1,3,5)-pyrimidinetrione, is **barbituric acid** (malonylurea). For this acid and its derivatives, see Vol. I, p. 630.

Alloxan, 2,4,5,6-pyrimidinetetrol, 2,4,5,6(1,3)-pyrimidinetetrone, produced by the cleavage of uric acid with concentrated nitric acid (Vol. I, p. 633).

HYDROXYPYRIMIDINECARBOXYLIC ACIDS. Uracil-4-carboxylic acid, 2,6-*dihydroxypyrimidinecarboxylic acid*, dec. 346°, by oxidation of 4-methyluracil; the ethyl ester (m.p. 189°) is synthesized from oxaloacetic ester and urea, according to method *1* (p. 288). It is identical with orotic acid (*Bachstez*, Ber. **60**, 1000), one of the compounds isolated from the mother liquor of lactose production [*Biscaro*, *Belloni*, C. **1905, II,** 63].

AMINOPYRIMIDINES (*Cyanoalkines*). (*Cf.* method *2*, p. 288). 2,4-**Dimethyl**-6-**aminopyrimidine**, *cyanomethine*, m.p. 180°; 2,4-**diethyl**-5-**methyl**-6-**aminopyrimidine**, *cyanoethine*, m.p. 189°; 2,4-**dibenzyl**-5-**phenyl**-6-**aminopyrimidine**, *cyanobenzyline*, m.p. 106° (*Kratz*, J.pr. **53**, 210).

2-**Amino**- and 6-**aminopyrimidine** and 2,6-**diaminopyrimidine**, from their halogen derivatives by reduction (*Gabriel*, Ber. **34**, 3362; *Büttner*, Ber. **36**, 2227). 2,4,6-**Triaminopyrimidine**, m.p. 246°, from 2,4,6-trichloropyrimidine with NH_3 at 200°, or from guanidine and malononitrile with sodium ethylate (*Traube*, Ber. **37**, 4544), reacts with HNO_2 to form nitrosotriaminopyrimidine, which can be reduced to 2,4,5,6-**tetraaminopyrimidine**. 4,5,6-**Triaminopyrimidine**, which gives *adenine* (Vol. I, pp. 641, 643) when heated with formic acid, is prepared from 4,5,6-triamino-2-thiopyrimidine by oxidation with H_2O_2; the latter compound is obtained from 4,6-**diamino**-2-**thiopyrimidine**, which is synthesized from malononitrile and thiourea. Thiourea and cyanoacetic ester give 4-**amino**-2-**thiopyrimidol**, which can be converted to 4,5-diamino-2-thiopyrimidol; when condensed with formic acid and oxidized (to remove the SH-group), the latter yields hypoxanthine (Vol. I, pp. 641, 642) (*Traube*, Ann. **331**, 64).

AMINOPYRIMIDOLS are prepared: (*1*) from β-oxocarboxylic acid esters with guanidine, *e.g.*, 4,5-**dimethyl**- and 4-**methyl**-5-**ethyl**-2-**amino**-6-**pyrimidol** from guanidine with methyl- and with ethylacetoacetic ester (*Schlenker*, Ber. **34**, 2835; *Byk*, Ber. **36**, 1915). (*2*) From amidines with cyanoacetic ester and Na ethylate, *e.g.*, 2-**methyl**- and 2-**phenyl**-6-**amino**-4-**pyrimidol** (*Traube*, *Herrmann*, Ber. **37**, 2267; Ger. Pat. 135371, 1901). 4-**Amino**-2,6-**pyrimidinediol**, by condensation of cyanoacetylurea in alkali (*Baum*, Ber. **41**, 525). 4,5-**Diamino**-2,6-**pyrimidinediol** and 5-**amino**-2,4,6-**pyrimidinetriol** (*uramil*) are used in the synthesis of uric acid (Vol. I, p. 639).

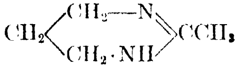
Cytosine, 4-*amino*-2(1)-*pyrimidone* or 4-*amino*-2-*pyrimidol*, was first obtained from thymus nucleic acid. Synthesis, properties: Vol. I, p. 628. Cytosine can be prepared with better yield from uracil over 2,6-dichloropyrimidine (*cf.* *Hilbert*, *Johnson*, Am. **52**, 1152). 5-**Methylcytosine** is a cleavage product of the nucleic acid of the tubercle bacillus (*Johnson*, *Coghill*, Am. **47**, 2838). 2,5-**Diamino**-4,6-**pyrimidinediol**, having a characteristic crystalline sulfate which is sparingly soluble in water, is identical with *divicine*, a product of the cleavage of *vicine* (from vetch) with 20% sulfuric acid [*Levene*, J.Biol.Chem. **18** (1914), 305; *Fischer*, Ber. **47**, 2611; *Levene*, *Senior*, J.Biol.Chem. **25** (1917), 607] (*cf.* the analogous formation of alloxanthine from *convicine*, Vol. I, p. 634).

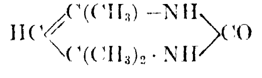
CHLOROPYRIMIDINES are formed from pyrimidols with $POCl_3$; they are important intermediates, since the chlorine atoms are easily replaced by NH_2, OR, SH, or H. When pyrimidine is treated with bromine the 5-position is substituted first (*Johnson*, *Joyce*, Am. **38**, 1557). 4,5-**Dimethyl**-2-**chloropyrimidine**, m.p. 38°, b.p. 223°; 2,4-**dimethyl**- and 2-**phenyl**-4-**methyl**-6-**chlorop**. (*Angerstein*, Ber. **34**, 3956; *Schmidt*, Ber. **35**, 1575). 4-**Methyl**-2,6-**dichlorop**., m.p. 47°, b.p. 219°; 4,5-**dimethyl**-2,6-**dichlorop**., m.p. 71°; 4-**methyl**-5-**ethyl**-2,6-**dichlorop**., m.p. 39° (*Schlenker*, Ber. **34**, 2825; *Byk*, Ber. **36**, 1915). 2,4,6-**Trichloropyrimidine**, m.p. 21°, b.p. 213°, from barbituric acid (*Gabriel*, *Colman*, Ber. **37**, 3657); 2,4,5,6-**tetrachloropyrimidine**, m.p. 70°, from dialuric acid

(*Fichter, Merckins*, Ber. **34**, 4176). Depending on the temperature, trichloropyrimidine reacts with NH_3 to give aminodichloro-, diaminochloro-, or triaminopyrimidine (see above). **2-Phenyl-5-chloropyrimidine**, m.p. 96°, and **2-phenyl-5-bromopyrimidine**, m.p. 104°, are obtained from their carboxylic acids, which are prepared from mucochloric and mucobromic acid with benzamidine (*Kunckell, Sarfert*, Ber. **35**, 3169).

HYDROXYPYRIMIDINECARBOXALDEHYDES. Uracil-4-carboxaldehyde (hydrate), m.p. over 300° (*Johnson, Cretcher*, Am. **37**, 2144). **Thymine-4-carboxaldehyde**, m.p. 205° (1 H_2O), by hydrolysis of the diethyl acetal of 2-ethylmercapto-4-thyminecarboxaldehyde (*Johnson, Cretcher*, J.Biol.Chem. **26**, 99). For the explanation of this synthesis, see p. 288. **Cytosine-4-carboxaldehyde**, m.p. 255° (dec.) (*Johnson, Matsuo*, Am. **41**, 810).

HYDROPYRIMIDINES. Tetrahydropyrimidines are obtained from 1,3-diamines with carboxylic acids or from 1,3-dibromides with carboxylic acid amides. **2-Methyltetrahydropyrimidine** (I), m.p. about 73°, b.p. 120–126° (20 mm.), from 1,3-propanediamine with acetic acid; **2,4,6-trimethyltetrahydropyrimidine**, *cis-* and *trans-*form: m.p. 73° and 102°, from the two forms of 2,4-pentanediamine with acetic acid (*Harries, Haga*, Ber. **32**, 1191; *Haga, Majima*, Ber. **36**, 334). **2-Phenyltetrahydropyrimidine**, from 1,3-dibromopropane and benzamidine (*Pinner*, Ber. **26**, 2122). **2-Phenyldihydro-5(4)-pyrimidone**, m.p. 91°, from diaminoacetone and benzoyl chloride (*Rügheimer, Mischel*, Ber. **25**, 1564; *Traube*, Ber. **27**, 277). **4,6,6-Trimethyldihydro-2(1)-pyrimidone** (II),

(I) 

 (II)

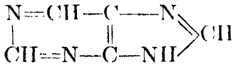
m.p. 194°, from N-(α,α-dimethyl-γ-oxobutyl)-urea, $NH_2CONHC(CH_3)_2 \cdot CH_2COCH_3$ (*Traube, Lorenz*, Ber. **32**, 3156).

1,3-Diphenylhexahydropyrimidine, m.p. 87°, from trimethylenedianiline with formaldehyde (*Scholz*, Ber. **32**, 2253).

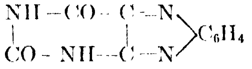
The **oxo** and **imino derivatives** of **di-**, **tetra-**, and **hexahydropyrimidines** are the tautomeric forms of mono-, di-, and trihydroxypyrimidines, aminopyrimidines and hydroxyaminopyrimidines (see above).

Purine and its derivatives contain a double ring of pyrimidine and imidazole. The purines are usually synthesized from 4,5-diaminopyrimidines or 4,5-aminopyrimidols (see above and Vol. I, pp. 638 *ff.*).

Alloxazine, 2,4(1,3)-*pyrimido*[4,5-*b*]*quinoxalinedione*, prepared from alloxan and *o*-phenylenediamine, has a ring system somewhat similar to that of purine (*Kühling*, Ber. **32**, 1650, and others):

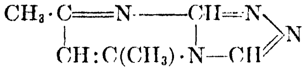


Purine

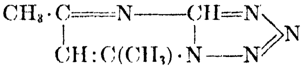


Alloxazine

Compounds containing a pyrimidine ring fused to a *s*-triazole or tetrazole ring are obtained by condensation of C-aminotriazole (p. 156) and C-aminotetrazole (aminotetrazotic acid) (p. 172) with 1,3-diketones or β-oxocarboxylic acid esters (*Bülow*, Ber. **42**, 4429; *Bülow, Haas*, Ber. **42**, 4638):

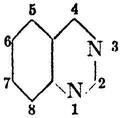


5,7-Dimethyl-*s*-triazolo[2,3-*a*]-pyrimidine

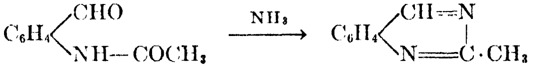


5,7-Dimethyltetrazolo[*a*]-pyrimidine

(2) **QUINAZOLINES.** The quinazolines are benzopyrimidines or benzo-1,3-diazines. They are isomeric with the phthalazines, the cinnolines (p. 285) and the quinoxalines (p. 299). Their formula may be derived from the quinoline or isoquinoline formula by replacement of a methine group by N:



Quinazolines are prepared from acyl derivatives of *o*-aminobenzaldehyde and of *o*-aminobenzyl ketones (*Bogert, McColm,* Am. **49,** 2650) by treatment with alcoholic ammonia (*Bischler, Lang,* Ber. **28,** 279):

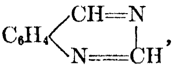


$$C_6H_4\left\langle\begin{array}{l}CHO\\ NH{-}COCH_3\end{array}\right. \xrightarrow{NH_3} C_6H_4\left\langle\begin{array}{l}CH{=}N\\ N{=}C\cdot CH_3\end{array}\right.$$

o-Acetamidobenzaldehyde 2-Methylquinazoline

Quinazolines are also obtained by oxidation of dihydroquinazolines with potassium ferricyanide (*Gabriel,* Ber. **36,** 810).

The quinazolines are stable tertiary bases which distill undecomposed. They add alkyl iodides. They are reduced by sodium and alcohol to dihydroquinazolines (*Bischler, Howell,* Ber. **26,** 1385). Oxidation with chromic acid in glacial acetic acid converts quinazolines in which the CH-group next to the benzene ring is free into oxodihydroquinazolines (or hydroxyquinazolines, p. 293). With mineral acids the pyrimidine ring is opened by hydrolysis.

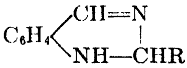
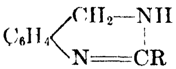
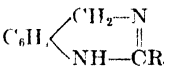
QUINAZOLINE, *benzopyrimidine,*  $C_6H_4\left\langle\begin{array}{l}CH{=}N\\ N{=}CH\end{array}\right.$, m.p. 48°, b.p. 243°, from dihydroquinazoline with potassium ferricyanide and from the condensation product of *o*-nitrobenzaldehyde with formamide by reduction with zinc dust and acetic acid (*Bogert, McColm,* Am. **49,** 2650). It adds methyl iodide at the 3-N-atom. This addition product is converted by aqueous potassium hydroxide to 3-methyl-3-quinazolinium hydroxide, $C_8H_6N_2(CH_3)OH$, m.p. 164°, which decomposes when distilled with aqueous potassium hydroxide into formic acid and α-methyliminotoluidine, $NH_2C_6H_4CH{:}NCH_3$ (*Gabriel, Colman,* Ber. **37,** 3650). With $KMnO_4$ quinazoline is oxidized mostly to 4,5-pyrimidinedicarboxylic acid (p. 289) (*loc. cit.*, p. 3646).

2-Methylquinazoline, m.p. 41°, b.p. 248°, from *o*-acetamidobenzaldehyde or 2-methyldihydroquinazoline (*Gabriel,* Ber. **36,** 810). **4-Methylquinazoline,** b.p. 260°, from its 2-carboxylic acid (*Bogert, Nabenhauer,* Am. **46,** 1932). **2,4-Dimethylquinazoline,** oil, b.p. 249° (hydrate, m.p. 71°), from *o*-acetamidoacetophenone with NH_3. **2-Phenylquinazoline,** m.p. 101°, is obtained from *o*-benzamidobenzaldehyde with NH_3, from 2-(aminobenzyl)-benzamide instead of the expected dihydro derivative (p. 293) and from 2-chloroquinazoline and benzene by the Friedel-Crafts method (Brit. Pat. 287179, 1928). **2-Methyl-4-phenylquinazoline,** $C_8H_4(CH_3)(C_6H_5)N_2$, m.p. 48°, from *o*-acetamidobenzophenone, is oxidized by chromic acid to 4-phenylquinazoline-2-carboxylic acid. As in quinaldine, the methyl group in the 2-position is very reactive (*Bogert, Nabenhauer,* Am. **46,** 1932).

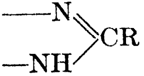
2-Phenylquinazoline-4-carboxylic acid, m.p. 151°, the analogue of atophan (*Bogert, Nabenhauer,* Am. **46,** 1702).

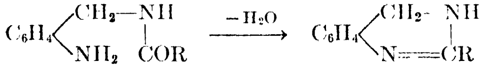
Chloroquinazolines are prepared from oxohydroquinazolines with PCl_5. **2-Chloro-** and **4-chloroquinazoline,** m.p. 108° and 96°, from 2(1)- and 4(3)-quinazolone; **2-chloro-4-phenylquinazoline,** m.p. 113°, from 4-phenyl-2(1)-quinazolone (*Gabriel, Stelzner,* Ber. **29,** 1310); **2,4-dichloroquinazoline,** m.p. 115°, from 2,4(1,3)-quinazolinedione (p. 296).

For quinazolines with partially hydrogenated pyrimidine rings, there are three possible structures:

(I) 
$C_6H_4\!<\!\begin{array}{l}CH{=}N\\ NH{-}CHR\end{array}$
(II) 
$C_6H_4\!<\!\begin{array}{l}CH_2{-}NH\\ N{=}CR\end{array}$
(III) 
$C_6H_4\!<\!\begin{array}{l}CH_2{-}N\\ NH{-}CR\end{array}$

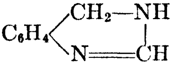
These are the 1,2-, 3,4-, and 1,4-dihydroquinazolines.

Dihydroquinazolines, containing the same atomic grouping,  $\begin{array}{l}{-}N\\ {-}NH\end{array}\!>\!CR$ as the benzimidazoles (p. 133), the *anhydro-bases* of *o-phenylenediamines*, may be considered as ring-homologues of the latter, the anhydro-bases of *o*-aminobenzylamines (Vol. III, p. 263). They are formed by elimination of water from the acyl derivatives of *o*-aminobenzylamine and its substitution products (*Gabriel, Jansen,* Ber. **24,** 3096; *Wolff,* Ber. **25,** 3037; *Paal,* J.pr. **48,** 537; **54,** 258; *Gabriel, Colman,* Ber. **37,** 3644). They are also synthesized from *p*-substituted aromatic amines, such as *p*-toluidine, with formaldehyde; the N,N′-diarylmethanediamines first formed are converted by a modification of the semidine rearrangement to *o*-aminobenzylamines, which react with the formic acid (from the formaldehyde) to give dihydroquinazolines (*Maffei,* Gazz. **58,** 261). The following equation illustrates the ring-synthesis:

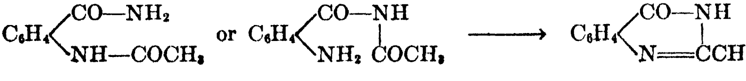

$$C_6H_4\!<\!\begin{array}{l}CH_2{-}NH\\ NH_2\quad COR\end{array} \xrightarrow{-H_2O} C_6H_4\!<\!\begin{array}{l}CH_2{-}NH\\ N{=}CR\end{array}$$

The reaction follows the same course if the acyl group is on the aromatic NH_2-radical (*Bischler,* Ber. **26,** 1891; *Widman,* J.pr. **47,** 343). Dihydroquinazolines are also formed by reduction of the corresponding *o*-nitrobenzylamine derivatives (*cf. Paal, Benker,* Ber. **32,** 1251; *Paal, Härtel,* Ber. **32,** 2057).

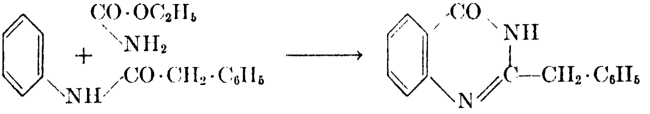
The dihydroquinazolines are rather strong bases, forming stable salts. The imine hydrogen is readily replaced by alkyl groups. When oxidized, they first give quinazolines, then quinazolones (hydroxyquinazolines). Distillation with zinc dust decomposes them, treatment with sodium and alcohol reduces them to tetrahydroquinazolines.

3,4-Dihydroquinazoline,  $C_6H_4\!<\!\begin{array}{l}CH_2{-}NH\\ N{=}CH\end{array}$, m.p. 127°, is obtained by reduction of N-formyl-*o*-nitrobenzylamine, by heating *o*-aminobenzylamine with formic acid (*Gabriel, Colman,* Ber. **37,** 3645) and by reduction of 2- and 4-chloroquinazoline and 2,4-dichloroquinazoline (see above) with glacial acetic acid and hydriodic acid (*Gabriel, Colman,* Ber. **38,** 3559). 3-**Methyl**-3,4-**dihydroquinazoline,** m.p. 92°, b.p. 309°, from *o*-aminobenzylmethylamine with formic acid. 3-**Phenyl**-3,4-**dihydroquinazoline,** m.p. 95°, from *o*-nitrobenzylformanilide or from *o*-aminobenzyl alcohol and formanilide (Ger. Pat. 113163, 1899). Diethoxy derivatives of this compound are local anesthetics (*Maffei,* Gazz. **59,** 3). 2-**Methyl**-3,4-**dihydroquinazoline,** from N-*o*-aminobenzylacetamide; 4-**phenyl**-3,4-**dihydroquinazoline,** m.p. 166°, from 2-chloro-4-phenylquinazoline by reduction (*Gabriel, Stelzner,* Ber. **29,** 1310).

4-OXO-3,4-DIHYDROQUINAZOLINES, β- or 4(3)-**QUINAZOLONES** (4-*hydroxyquinazolines*), are synthesized from acyl derivatives of *o*-aminobenzamide (this is analogous to the formation of dihydroquinazolines from acyl derivatives of *o*-aminobenzylamines):

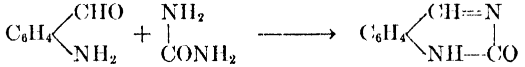

$$C_6H_4\!<\!\begin{array}{l}CO{-}NH_2\\ NH{-}COCH_3\end{array} \text{ or } C_6H_4\!<\!\begin{array}{l}CO{-}NH\\ NH_2\quad COCH_3\end{array} \longrightarrow C_6H_4\!<\!\begin{array}{l}CO{-}NH\\ N{=}CCH_3\end{array}$$

Similar products are obtained by heating acylanthranils or acyl derivatives of anthranilic acid ester with NH_3 or primary amines, anthranilonitrile with fatty acid amides, and anthranilic acid thiamide or anthranilonitrile with carboxylic acids or their anhydrides (*Bogert, Breneman, Hand,* Am. **25,** 372; *Bogert, Gortner, Amend,* Am. **33,** 949; *Heilbron, Kitchen, Parkes, Sutton,* J. **127,** 2167) (Vol. III, p. 328). Another type of ring-closure is illustrated by the synthesis of 2-*benzyl*-4(3)-*quinazolones* from N-arylphenacetamides and urethans in boiling toluene solution [*Aggarwal, Das, Ray,* J.IndianChem.Soc. **6,** (1930), 717]:



Besides these synthetic methods, quinazolones are also prepared by oxidation of quinazolines and dihydroquinazolines.

2-OXODIHYDROQUINAZOLINES, 2(1)- or α-**QUINAZOLONES,** are formed by heating *o*-aminobenzaldehydes and *o*-aminobenzyl ketones with urea (*Gabriel, Stelzner,* Ber. **29,** 1300):



$$\mathrm{C_6H_4}\!<\!\begin{matrix}\mathrm{CHO}\\ \mathrm{NH_2}\end{matrix} + \begin{matrix}\mathrm{NH_2}\\ |\\ \mathrm{CONH_2}\end{matrix} \longrightarrow \mathrm{C_6H_4}\!<\!\begin{matrix}\mathrm{CH{=}N}\\ \quad|\\ \mathrm{NH{-}CO}\end{matrix}$$

The quinazolones have both weakly basic and phenolic properties, and therefore may also be considered as hydroxyquinazolines. With alkyl iodides they give N-alkyl derivatives of the keto-form; the isomeric alkoxyquinazolines are obtained from the chloroquinazolines (p. 292) with sodium alcoholates (*Bogert, May,* Am. **31,** 507).

4(3)-**Quinazolone,** 4-*oxo*-3,4-*dihydroquinazoline,* m.p. 214°, from anthranilic acid with formamide and from its carboxylic acid (see below) (*Knape,* J.pr. **43,** 215; *v. Niementowski,* J.pr. **51,** 564), yields with methyl iodide 3-**methyl**-4(3)-**quinazolone,** $C_8H_5ON_2 \cdot CH_3$, m.p. 71°.

2-**Methyl**-4(3)-**quinazolone,** m.p. 232°, is prepared from *o*-acetamidobenzamide or N-*o*-aminobenzoylacetamide (see above), from anthranilic acid and acetonitrile (*Bogert, Gotthelf,* Am. **22,** 129) and by oxidation of 2-methylquinazoline (*Bischler, Lang,* Ber. **28,** 279). Like picoline and quinaldine, it condenses with benzaldehyde to give 2-styryl-4(3)-quinazolone (*Bogert, Beal, Amend,* Am. **32,** 1654; *Heilbron, Kitchen, Parkes, Sutton,* J. **127,** 2167). 2-**Phenyl**-4(3)-**quinazolone,** $C_8H_5(C_6H_5)N_2O$, m.p. 236°, from phenylquinazoline by oxidation, from *o*-benzoylaminobenzamide and from anthranilic acid ester by condensation with benzimidoethyl ether (Vol. III, p. 308, and *Finger, Schupp,* J.pr. **74,** 154). 3-**Phenyl**-4(3)-**quinazolone,** m.p. 139°, by oxidation of 3-phenyldihydroquinazoline (*Paal, Krecke,* Ber. **24,** 3055) or by condensation of anthranilic acid and formanilide [*Kulisch,* Z. österr.Apoth.-V. **37** (1899), 138].

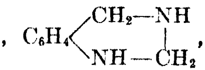
4-**Oxo**-3,4-**dihydroquinazoline**-2-**carboxylic acid,** m.p. 230° (with evolution of CO_2) is formed by rearrangement of cyanoxanilic acid, $CN \cdot C_6H_4NH \cdot COCOOH$ and by the action of alcoholic ammonia on ethoxalylanthranil. Its nitrile is produced by the reaction between cyanogen and anthranilic acid in aqueous solution (*Reissert, Grube,* Ber. **42,** 3713; *Bogert, Gortner,* Am. **32,** 119).

2(1)-**Quinazolone,** α-*quinazolone,* is prepared from *o*-aminobenzaldehyde and urea and also by the oxidation of 2-imino-1,2-dihydro-3,1,4-benzothiazine (p. 278) with barium permanganate. 4-**Phenyl**-2(1)-**quinazolone,** m.p. 251°, from *o*-aminobenzophenone and urea (*Gabriel, Stelzner,* Ber. **29,** 1310).

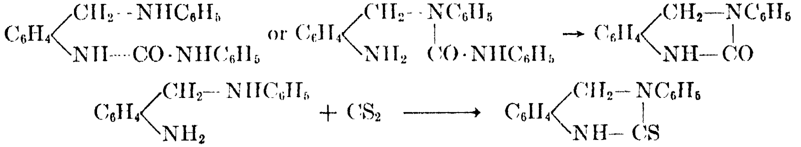
3(N)-**Aminoquinazolones** have been obtained from *o*-aminobenzohydrazides (*Heller,* J.pr. **111,** 36).

TETRAHYDROQUINAZOLINES have been prepared by reduction of quinazolines, dihydroquinazolines, and thiotetrahydroquinazolines (see below); they are also formed by condensation of *o*-aminobenzylamines with aldehydes (*Busch,* J.pr. **53,** 414; **55,**

356). They can be decomposed without difficulty to *o*-derivatives of benzene.

1,2,3,4-Tetrahydroquinazoline,  $C_6H_4\left\langle\begin{matrix}CH_2-NH\\ NH-CH_2\end{matrix}\right.$, m.p. 79°, from *o*-aminobenzylamine and formaldehyde or from dihydroquinazoline by reduction with sodium amalgam (*Gabriel,* Ber. **36,** 811). **3-Phenyltetrahydroquinazoline,** $C_6H_4(C_2H_5N\cdot C_6H_5)$, m.p. 119°, is obtained from *o*-aminobenzylaniline and formaldehyde as well as from phenyldihydro- and phenylthiotetrahydroquinazoline (*Busch,* Ber. **25,** 2858) and 3-phenyl-4(3)-quinazolone by reduction. **2-Phenyltetrahydroquinazoline,** m.p. 100° (*Wolff,* Ber. **25,** 3033). **4-Phenyltetrahydroquinazoline,** see *Gabriel, Stelzner,* Ber. **29,** 1308. **1,3-Dibenzoyl-2,4-dimethyltetrahydroquinazoline,** $C_8H_6(CH_3)_2N_2(COC_6H_5)_2$, m.p. 155° (*Bischler, Howell,* Ber. **26,** 1385).

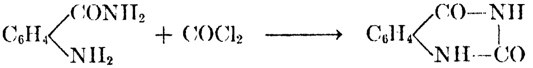
2-**OXO-** and 2-**THIOTETRAHYDROQUINAZOLINES** correspond to the cyclic phenyleneureas and thioureas (oxo- and thiobenzimidazolines, p. 135) and, like these, are obtained from *o*-aminobenzylamines with $COCl_2$ or CS_2, or from the urea derivatives of *o*-aminobenzylamines by elimination of ammonia or amine (*Busch,* Ber. **25,** 2856; *Paal,* J.pr. **48,** 537):



$$C_6H_4\left\langle\begin{matrix}CH_2-NHC_6H_5\\ NH-CO\cdot NHC_6H_5\end{matrix}\right. \text{ or } C_6H_4\left\langle\begin{matrix}CH_2-NC_6H_5\\ NH_2\quad CO\cdot NHC_6H_5\end{matrix}\right. \longrightarrow C_6H_4\left\langle\begin{matrix}CH_2-NC_6H_5\\ NH-CO\end{matrix}\right.$$

$$C_6H_4\left\langle\begin{matrix}CH_2-NHC_6H_5\\ NH_2\end{matrix}\right. + CS_2 \longrightarrow C_6H_4\left\langle\begin{matrix}CH_2-NC_6H_5\\ NH-CS\end{matrix}\right.$$

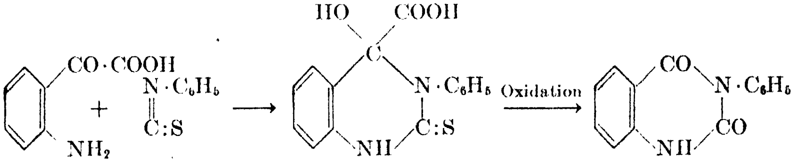
2,4(1,3)-**QUINAZOLINEDIONES, dioxotetrahydroquinazolines,** are similarly prepared from *o*-aminobenzamides with $COCl_2$, ClCOOR, and the like, or from urea derivatives of *o*-aminobenzamide, or from anthranilic acids:



$$C_6H_4\left\langle\begin{matrix}CONH_2\\ NH_2\end{matrix}\right. + COCl_2 \longrightarrow C_6H_4\left\langle\begin{matrix}CO-NH\\ NH-CO\end{matrix}\right.$$

2,4(1,3)-Quinazolinedione

Another synthesis of a different type consists in the reaction between phenyl isothiocyanate and isatinic acid (*Reissert, Schaaf,* Ber. **59,** 2494):



Oxo- and thiotetrahydroquinazolines are neutral substances. Their formation from imino and thio derivatives of 3,1,4-benzoxazine by heating with aromatic amines was mentioned on p. 273. When oxidized, they yield quinazolinediones, which are also produced by the oxidation of iminodihydro-3,1,4-benzoxazines (*Paal, Vanvolxem,* Ber. **27,** 2420). The quinazolinediones have acidic properties; they dissolve only in alkalis, and with PCl_5 they give dichloroquinazolines.

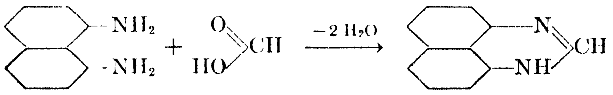
3-Phenyl-3,4-dihydro-2(1)-quinazolone, $C_8H_7\cdot ON_2\cdot C_6H_5$, m.p. 189° (*Ladenburg,* Ber. **27,** 75). **4-Phenyl-3,4-dihydro-2(1)-quinazolone,** m.p. 193°, is prepared from *o*-aminobenzohydrol with urea, and also from the corresponding phenylthiotetrahydroquinazoline (*Gabriel, Stelzner*, Ber. **29**, 1307; *Hanschke*, Ber. **32**, 2026).

3,4-Dihydro-2(1)-quinazolinethione, $C_8H_8SN_2$, m.p. 211°. **3-Phenyl-3,4-dihydro-2(1)-quinazolinethione**, $C_8H_7SN_2 \cdot C_6H_5$, m.p. 260° (*Paal, Commerell*, Ber. **27**, 2432). **4-Phenyl-3,4-dihydro-2(1)-quinazolinethione**, m.p. 230°, from *o*-aminobenzohydrol and thiocyanic acid (*Gabriel, Stelzner*, Ber. **29**, 1305).

2,4(1,3)-Quinazolinedione, *benzoyleneurea* (see above), m.p. over 360°, sublimable, is obtained from anthranilic acid with potassium cyanate, and from pseudoisatoxime (p. 76) by a *Beckmann* rearrangement (*Diels, Wagner*, Ber. **45**, 882; *Heller*, Ber. **49**, 2774). **N-Phenyl-2,4(1,3)-quinazolinedione**, m.p. 272° (*Kunckell*, Ber. **43**, 1237). **2-Thio-1,2-dihydro-4(3)-quinazolone**, m.p. 284°, from anthranilic acid ester and thiocyanic acid (*Rupe*, Ber. **30**, 1098).

5,6,7,8-Tetrahydroquinazolines have been prepared from 2-acetylcyclohexanone and 2-oxocyclohexanecarboxylic acid ester and amidines, according to method *1* (p. 288) [*Mitter, Bhattacharya*, Quart. J. Indian Chem. Soc. **4** (1927), 149].

PERIMIDINES, 1-*benzo*[*de*]*quinazolines*, contain a pyrimidine ring joining the peri positions of a naphthalene ring. They correspond to the benzimidazoles (p. 131) and are formed in an analogous way by condensation of 1,8-naphthalenediamine with carboxylic acids (*Sachs*, Ann. **365**, 53; *Sachs, Forster*, Ber. **44**, 1738; Ger. Pat. 252772, 1911, Frdl. **XI**, 315; Ger. Pat. 255823, 1911, Frdl. **XI**, 493; Ger. Pat. 253239, 1912, Frdl. **XI**, 495, and others):



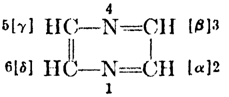
Perimidine

Perimidine forms green crystals, m.p. about 220°. Analogous compounds in the anthracene series have been obtained from 1-aminoanthraquinone by reaction with urethan, formamide and the like.

A large number of **dibenzoquinazolinediones** (anthraquinonepyrimidines) are known (Ger. Pats. 185548, 1906, Frdl. **IX**, 730; 220314, 1908, Frdl. **IX**, 742). Some of the corresponding *Py*-oxo derivatives (anthraquinonepyrimidones) (Ger. Pat. 205035, Frdl. **IX**, 740) are used as dyes, *e.g.*, *alizarin geranol B* (see *Fierz-David*, Künstliche organische Farbstoffe, p. 626).

Pyrimidoquinazolines, *benzodipyrimidines*, have also been prepared; they are sometimes called *naphthotetrazines*.

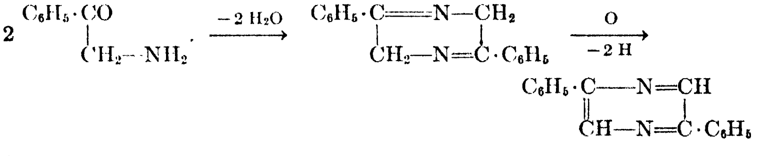
(c) 1,4-Diazines



$$\begin{array}{ccccc} & & 4 & & \\ 5[\gamma]\ \mathrm{HC} & - & \mathrm{N} & = & \mathrm{CH}\ [\beta]3 \\ \| & & & & | \\ 6[\delta]\ \mathrm{HC} & - & \mathrm{N} & = & \mathrm{CH}\ [\alpha]2 \\ & & 1 & & \end{array}$$

(1) **PYRAZINES** are 1,4-diazines; their ring is like that of pyridine, but with the methine group in the 4-position replaced by N.

Pyrazines are formed: (*1*) From α-aminoaldehydes and α-aminoketones. Two molecules condense with elimination of water to give dihydropyrazines, which are oxidized even by the air to pyrazines (*cf. Gabriel*, Ber. **41**, 1128):

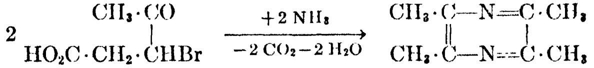


$$2\ \begin{array}{l} C_6H_5\cdot CO \\ | \\ CH_2-NH_2 \end{array} \xrightarrow{-2\,H_2O} \begin{array}{l} C_6H_5\cdot C=N-CH_2 \\ | \qquad\qquad\quad | \\ CH_2-N=C\cdot C_6H_5 \end{array} \xrightarrow[-2\,H]{O} \begin{array}{l} C_6H_5\cdot C-N=CH \\ \| \qquad\qquad\quad | \\ CH-N=C\cdot C_6H_5 \end{array}$$

Because of their relation to the α-aminoaldehydes and α-aminoketones, the pyrazines have also been called aldines and ketines.

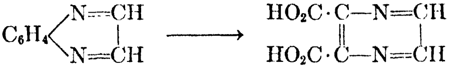
Solutions in which aminoketones have been produced by reduction of isonitroso-ketones can be used directly for the preparation of pyrazines by distillation with $HgCl_2$ (*Wolff*, Ber. **26**, 1832; *Gabriel, Pinkus*, Ber. **26**, 2207).

(*2*) Amino-ketones are formed as intermediates in the synthesis of pyrazines from α-chloro- and α-bromo-keto derivatives with ammonia. β-Bromolevulinic acid and ammonia, on elimination of water and CO_2, yield tetramethylpyrazine:



$$2\begin{array}{l} CH_3\cdot CO \\ \quad\;| \\ HO_2C\cdot CH_2\cdot CHBr \end{array} \xrightarrow[-2\,CO_2-2\,H_2O]{+2\,NH_3} \begin{array}{l} CH_3\cdot C{-}N{=}C\cdot CH_3 \\ \qquad\,\| \qquad\;\; | \\ CH_3\cdot C{-}N{=}C\cdot CH_3 \end{array}$$

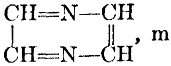
(*3*) 2,3-Pyrazinedicarboxylic acid derivatives have been obtained by the oxidative decomposition of quinoxaline (p. 301) and its homologues with $KMnO_4$ (*Gabriel, Sonn*, Ber. **40**, 4850):



Pyrazines occur among the fermentation products of beet sugar juice. 2,5-Dimethyl- and trimethylpyrazine have been isolated from fusel oil. Pyrazines (pyrazine, methyl- and dimethylpyrazine) are also obtained by the action of ammonia on grape sugar (*Bamberger, Einhorn*, Ber. **30**, 224; *Brandes, Stoehr*, J.pr. **54**, 481).

The pyrazines give a neutral reaction with litmus. They are usually weak, monoacid bases, forming easily dissociated salts with acids. Like pyridine (p. 201), they give characteristic, sparingly soluble compounds with metal salts, such as $HgCl_2$ and $AuCl_3$. With methyl iodide they give addition products.

The pyrazines are reduced by sodium to piperazines, hexahydropyrazines, which are analogous to the piperidines. Alkylpyrazines are oxidized by potassium permanganate to pyrazinecarboxylic acids, which are readily decarboxylated.

PYRAZINE (*piazine*), , m.p. 57°, b.p. 115° (*Tschitschibabin, Schtschukina*, Ber. **62**, 1075), sublimes even at room temperature, and has an odor like heliotrope. It is prepared from aminoacetaldehyde or aminoacetal by distillation with mercuric chloride solution, from pyrazinecarboxylic acids by decarboxylation, and from piperazine (p. 299) by distillation with zinc dust (*Wolff, Marburg*, Ann. **363**, 216). Gold salt, m.p. 245°; picrate, m.p. 156°.

Methylpyrazine, b.p. 135°, from its carboxylic acid (*Stoehr*, J.pr. **51**, 449), is the principal constituent of the bases obtained from grape sugar with ammonia (see above). 2,3-**Dimethylpyrazine,** from diacetyl and ethylenediamine and also from its dicarboxylic acid (see below) (*Gabriel, Sonn*, Ber. **40**, 4855). 2,5-**Dimethylpyrazine,** *ketine*, b.p. 153°, is prepared by reduction of isonitrosoacetone; it is formed when glycerol is heated with ammonia salts, together with pyridine bases (p. 198) and other alkylated pyrazines, such as 2-**methyl**-5,6-**diethylpyrazine,** b.p. 179° (*Stoehr*, Ber. **24**, 4105; J.pr. **47**, 439). 2,6-**Dimethylpyrazine,** m.p. 48°, b.p. 155° (*Brandes, Stoehr*, J.pr. **54**, 492). **Trimethylpyrazine,** b.p. 172°, is produced by heating the methyl bromide addition product of 2,5-dimethylpyrazine (*Brandes, Stoehr*, J.pr. **53**, 501). **Tetramethylpyrazine,** m.p. 86° (+3 H_2O, 75°), b.p. 190°, picrate m.p. 192°, from β-bromolevulinic acid with NH_3 (see above), from isonitrosolevulinic acid (*Thal*, Ber. **25**, 1723), or from the monoxime of biacetyl by reduction in alkaline solution (*Wallach*, Nachr. Ges. Wiss. Göttingen **1927**, 238).

Like picoline, quinaldine, and similar compounds, the methylpyrazines condense with benzaldehyde or chloral with elimination of water, forming products such as $(C_4H_2N_2)[2,5](CH{:}CHC_6H_5)_2$ (*Franke*, Ber. **38**, 3724).

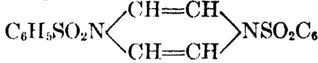
2,5-Diphenylpyrazine, m.p. 196°, is prepared from α-aminoacetophenone with intermediate formation of its dihydro derivative and, together with the isomeric

2,6-diphenylpyrazine, m.p. 90°, from α-chloro- or α-bromoacetophenone by treatment with ammonia (*Tutin*, J. **97**, 2495). 2,5-Diphenyl- and 2,6-diphenylpyrazine have also been obtained from N-dibenzyldihydro-2,5- and 2,6-diphenylpyrazine (see below) by elimination of toluene (*Mason*, *Winder*, J. **63**, 1355). **2,5-Diphenyl-3,6-dimethylpyrazine**, m.p. 126°, from α-isonitroso-α-phenylacetone (*Kolb*, Ann. **291**, 253) and from its dihydro derivative (see below) (*Gabriel*, Ber. **41**, 1150). **Tetraphenylpyrazine**, *tetraphenylaldine*, m.p. 246°, is obtained from the monooxime or dioxime of benzil (Vol. III, p. 566) (*Feist*, Ber. **27**, 213).

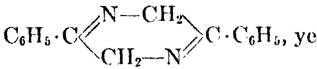
The **PYRAZINECARBOXYLIC ACIDS** are generally obtained by oxidation of alkylpyrazines with $KMnO_4$. They give yellow, red, or red-violet colorations with ferrous sulfate.

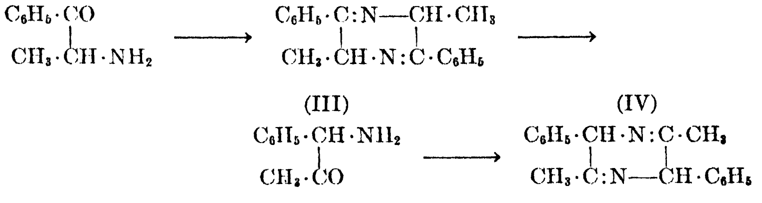
Pyrazinecarboxylic acid, m.p. 230° (dec.). **2,5-Pyrazinedicarboxylic acid** ($+2\ H_2O$), m.p. 256° (dec.), and **pyrazinetetracarboxylic acid**, m.p. 205° (dec.), are prepared from the methylated pyrazines with $KMnO_4$. **2,3-Pyrazinedicarboxylic acid**, m.p. 193° (dec.), and **5,6-dimethylpyrazine-2,3-dicarboxylic acid**, m.p. 200° (dec.), are formed by oxidation of quinoxaline (p. 301) and dimethylquinoxaline (*Gabriel*, *Sonn*, Ber. **40**, 4850). **Pyrazinetricarboxylic acid**, m.p. 190° (dec.), anhydrous.

1,4-DIHYDROPYRAZINES are obtained from α-alkylamino-ketones $RHN{-}CH_2{\cdot}CO{\cdot}R$, or from α-bromo-ketones with primary amines. When aniline is used in the latter synthesis, the isomeric indoles (p. 61) are also formed.

1,4-Dibenzenesulfonyldihydropyrazine,  m.p. 163°, from benzenesulfonamidoacetal (*Marckwald*, *Ellinger*, Ber. **26**, 98). Several dihydropyrazines, such as **1,4-dibenzyl-2,5-diphenyldihydropyrazine**, m.p. 163°, and **1-benzyl-2,6-diphenyldihydropyrazine**, have been obtained by condensation of benzylamine with α-bromoacetophenone.

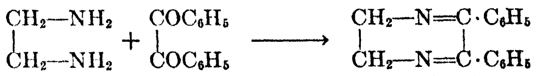
2,5-DIHYDROPYRAZINES are the primary condensation products of α-aminoaldehydes and α-amino-ketones (p. 296). When heated with mineral acids they decompose to the α-aminoaldehydes or ketones. Oxidizing agents, even the oxygen of the air, convert them to the corresponding pyrazines (*Gabriel*, Ber. **41**, 1128).

2,5-Diphenyl-3,6-dihydropyrazine,  yellow flakes, m.p. 116°, from α-aminoacetophenone. **2,5-Diphenyl-3,6-dimethyl-3,6-dihydropyrazine** (II below), m.p. 100°, from α-aminopropiophenone (I), is decomposed by hydrolysis with hydrochloric acid principally to the hydrochloride of α-amino-α-phenylacetone (III), which, precipitated from its salt by alkalis, condenses to **2,5-diphenyl-3,6-dimethyl-2,5-dihydropyrazine** (IV):

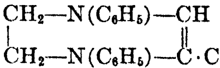


These isomeric dihydropyrazine derivatives give the same diphenyldimethylpyrazine when oxidized (see above).

2,3-DIHYDROPYRAZINES are formed from 1,2-diketones with ethylenediamine (*Bischoff*, Ber. **22**, 346; *Mason*, J. **63**, 1284):



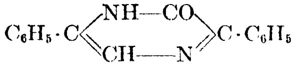
5,6-Diphenyl-2,3-dihydropyrazine

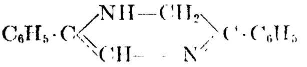
1,2,4-Triphenyltetrahydropyrazine, 

$$\begin{array}{l} CH_2—N(C_6H_5)—CH \\ | \qquad\qquad\qquad\quad \| \\ CH_2—N(C_6H_5)—C\cdot C_6H_5 \end{array}$$

, m.p. 131°, from N,N'-diphenylethylenediamine with α-bromoacetophenone [*Garzino*, Atti accad. sci. Torino, **27** (1892)]. **1,2,3-Triphenyltetrahydropyrazine,** from N-phenylethylenediamine and benzoin (*Gabriel, Eschenbach*, Ber. **31**, 1582).

3,6-Diphenyl-2(1)-pyrazinone (I), m.p. 197°, is produced by the action of gaseous hydrogen chloride on an ethereal solution of benzaldehyde cyanohydrin. When distilled with zinc dust, it is reduced to 2,5-diphenylpyrazine, but with HI and phosphorus it gives 2,5-**diphenyl**-3,4-**dihydropyrazine** (II), m.p. 164° (*Japp, Knox*, J. **87**, 701; *McCombie, Parry*, J. **95**, 584).

(I) 

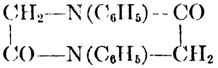
 (II)

For 2,5-**dimethyldihydropyrazine**-3,6-**dicarboxylic acid dianilide**, m.p. 218°, from azo dyes (*Hansa yellow*), see *Fierz-David, Ziegler*, Helv. **11**, 776.

PIPERAZINES, hexahydropyrazines, have been discussed as cyclic dialkyleneimines (Vol. I, p. 387). Besides the syntheses described there, piperazines may also be prepared by reduction of pyrazines with Na and alcohol (*Wolff*, Ber. **26**, 724). 2-**Methylpiperazine**, $C_4H_9(CH_3)N_2$, b.p. 155°; 2,5-**dimethylpiperazine** which is also obtained from lactimide, 3,6-*dimethyl*-2,5-*piperazinedione*, by reduction with Na and alcohol (*Hoyer*, Z.physiol.Chem. **34**, 347). Di- and polyalkylpiperazines exist in two stereoisomeric forms: for di-, tri-, and tetramethylpiperazine, see *Stoehr*, J.pr. **55**, 49. 1,4-**Dinitropiperazine**, $NO_2\cdot N(CH_2CH_2)_2\cdot N\cdot NO_2$, m.p. 215°, is formed by the action of fuming nitric acid on 1,4-dibenzenesulfonylpiperazine (*Sohn*, Rec. **28**, 68). 1,4-**Dimethylpiperazine**, b.p. 132° (*v. Braun, Kirschbaum*, Ber. **52**, 2265).

1,4-**Diphenylpiperazine**, m.p. 163°, is synthesized from 1,2-dibromoethane and aniline (*Bischoff*, Ber. **22**, 1777). 1,4-**Dibenzylpiperazine**, m.p. 92°, is obtained from N-β-bromoethylbenzylamine with KOH (*Gabriel, Stelzner*, Ber. **29**, 2384).

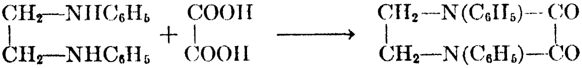
2,5-**PIPERAZINEDIONES** are cyclic double amides, which were treated in connection with the α-aminocarboxylic acids (Vol. I, pp. 387, 447). 1,4-**Diphenyl**-2,5-**piperazinedione**:



$$\begin{array}{l} CH_2—N(C_6H_5)—CO \\ | \qquad\qquad\qquad\quad | \\ CO—N(C_6H_5)—CH_2 \end{array}$$

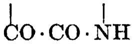
from N-phenylglycine. For stereoisomeric piperazinediones, see *Tigerstedt*, Ber. **25**, 2919; *Trapesonzjanz*, Ber. **25**, 3275; *Fischer, Raske*, Ber. **39**, 3981, and others.

2,3-**Piperazinediones** are prepared by condensation of oxalic acid with ethylenediamine derivatives (*Bischoff, Nastvogel*, Ber. **23**, 2028):



$$\begin{array}{l} CH_2—NHC_6H_5 \\ | \\ CH_2—NHC_6H_5 \end{array} + \begin{array}{l} COOH \\ | \\ COOH \end{array} \longrightarrow \begin{array}{l} CH_2—N(C_6H_5)—CO \\ | \qquad\qquad\qquad\quad | \\ CH_2—N(C_6H_5)—CO \end{array}$$

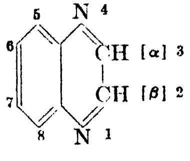
1,4-Diphenyl-2,3-piperazinedione

This diphenylpiperazinedione is oxidized by chromic acid to a piperazinetetrone. The simplest **piperazinetetrone,** 

$$\begin{array}{l} NH\cdot CO\cdot CO \\ | \qquad\qquad | \\ CO\cdot CO\cdot NH \end{array}$$

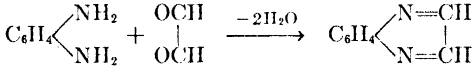
, was obtained by the action of sodium alcoholate on oxamic acid ester (*de Mouilpied, Rule*, J. **95**, 549).

(2) QUINOXALINES, 1,4-Benzodiazines:



Like the benzimidazoles, the quinoxalines are condensation products of *o*-diamines. The formula of quinoxaline may be derived from that of quinoline by replacement of the 4-methine group by nitrogen. This relation together with its synthesis from glyoxal and *o*-phenylenediamine was responsible for the name quinoxaline (*Hinsberg*) given to this bicyclic ring system. The quinoxalines are prepared:

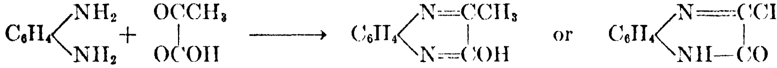
1. From *o*-phenylenediamines with glyoxal and other 1,2-dioxo compounds or their oximes (*Hinsberg*, Ann. **237**, 327):



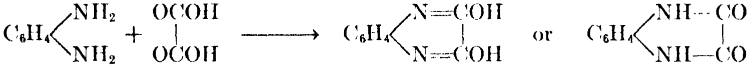
$$C_6H_4\left<\begin{array}{l}NH_2\\NH_2\end{array}\right. + \begin{array}{c}OCH\\|\\OCH\end{array} \xrightarrow{-2H_2O} C_6H_4\left<\begin{array}{l}N{=}CH\\ \quad\ |\\N{=}CH\end{array}\right.$$

Benzil gives 2,3-diphenylquinoxaline, dihydroxytartaric acid gives 2,3-quinoxalinedicarboxylic acid, *etc.* The reaction is completed rapidly and at low temperatures.

α-Oxo carboxylic acids, such as pyruvic acid and mesoxalic acid, yield quinoxalinols, while oxalic acid gives quinoxalinediols (*cf. Meyer*, Ber. **30**, 768):



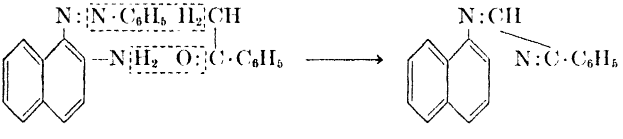
$$C_6H_4\left<\begin{array}{l}NH_2\\NH_2\end{array}\right. + \begin{array}{c}OCCH_3\\|\\OCOH\end{array} \longrightarrow C_6H_4\left<\begin{array}{l}N{=}CCH_3\\ \quad\ |\\N{=}COH\end{array}\right. \text{ or } C_6H_4\left<\begin{array}{l}N{=}CCH_3\\ \quad\ |\\NH{-}CO\end{array}\right.$$



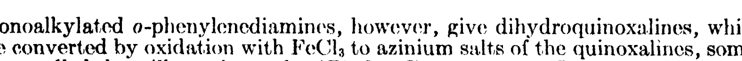
$$C_6H_4\left<\begin{array}{l}NH_2\\NH_2\end{array}\right. + \begin{array}{c}OCOH\\|\\OCOH\end{array} \longrightarrow C_6H_4\left<\begin{array}{l}N{=}COH\\ \quad\ |\\N{=}COH\end{array}\right. \text{ or } C_6H_4\left<\begin{array}{l}NH{-}CO\\ \quad\ |\\NH{-}CO\end{array}\right.$$

o-Naphthalenediamines react like *o*-phenylenediamine, forming *benzoquinoxalines*. *s*-Tetraaminobenzenes give *pyrazino[g]quinoxalines*, benzo-*bis*-*p*-diazines.

Quinoxalines are prepared without difficulty from the readily obtainable *o*-amino-azo compounds by treatment with aliphatic-aromatic ketones (such as acetophenone) (*Crippa*, Gazz. **59**, 330):

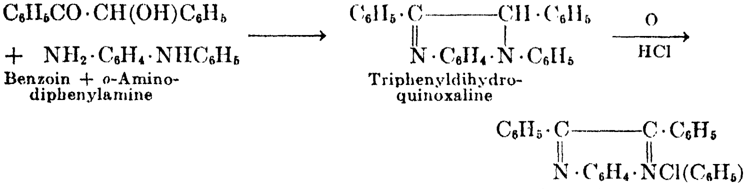


2. α-Chloroketones, α-formyl-alcohols and α-oxo alcohols, such as benzoin, furoin, arabinose, and glucose, condense with *o*-phenylenediamines, with elimination of H_2O and H_2, to form quinoxalines:



$$C_6H_4\left<\begin{array}{l}NH_2\\NH_2\end{array}\right. + \begin{array}{c}ClCH_2\\|\\OCCH_3\end{array} \longrightarrow C_6H_4\left<\begin{array}{l}N{=}CH\\ \quad\ |\\N{=}CCH_3\end{array}\right. + H_2O + HCl + H_2$$

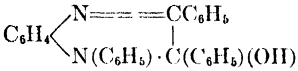
Monoalkylated *o*-phenylenediamines, however, give dihydroquinoxalines, which are converted by oxidation with $FeCl_3$ to azinium salts of the quinoxalines, sometimes called the stilbazonium salts (*Fischer*, Ber. **24**, 719; *Kehrmann, Messinger*, Ber. **24**, 1875; **25**, 1627):



$$\begin{array}{l}C_6H_5CO\cdot CH(OH)C_6H_5\\+\ NH_2\cdot C_6H_4\cdot NHC_6H_5\end{array} \longrightarrow \begin{array}{l}C_6H_5\cdot C\text{———}CH\cdot C_6H_5\\ \quad\ \| \qquad\qquad\ |\\ \quad N\cdot C_6H_4\cdot N\cdot C_6H_5\end{array} \xrightarrow[HCl]{O} \begin{array}{l}C_6H_5\cdot C\text{———}C\cdot C_6H_5\\ \quad\ \| \qquad\qquad\ \|\\ \quad N\cdot C_6H_4\cdot NCl(C_6H_5)\end{array}$$

Benzoin + *o*-Aminodiphenylamine — **Triphenyldihydroquinoxaline** — **Triphenylquinoxalinium chloride**

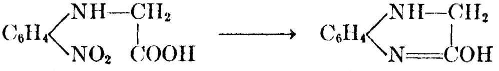
The reaction of monoalkylated or phenylated *o*-diamines on 1,2-diketones produces azinium salts directly. The bases corresponding to these salts are very unstable; they rearrange to pseudo-bases, such as:



$$C_6H_4\left\langle\begin{array}{l}N{=\!=}\;{=\!=}CC_6H_5\\ \qquad\qquad\;\;|\\ N(C_6H_5)\cdot C(C_6H_5)(OH)\end{array}\right.$$

from which the azinium salts are regenerated with acids (*Jacobson, Fischer*, Ber. **25**, 1010; *Witt, Helmolt*, Ber. **27**, 2355; *Kehrmann, Natcheff*, Ber. **31**, 2425; *Kehrmann, Woulfson*, Ber. **32**, 1042); see also the analogous behavior of the alkylquinolinium hydroxides, p. 230.

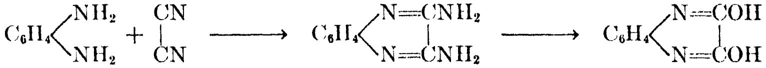
3. N-*o*-Nitrophenyl-α-amino-fatty acids reduce to 2-*hydroxy*-3,4-*dihydroquinoxalines*, which are also formed from *o*-phenylenediamine and α-halogen-fatty acids (*cf. Hinsberg*, Ann. **292**, 250):



$$C_6H_4\left\langle\begin{array}{l}NH{-}CH_2\\ \qquad\;\;|\\ NO_2\;\;COOH\end{array}\right. \longrightarrow C_6H_4\left\langle\begin{array}{l}NH{-}CH_2\\ \qquad\;\;|\\ N{=\!=}COH\end{array}\right.$$

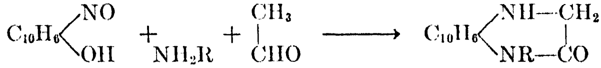
o-Nitrophenylglycine 1,2-Dihydroquinoxalinol-3

4. *o*-Phenylenediamines condense with dicyanogen to *diaminoquinoxalines*, which are converted to quinoxalinediols by dilute hydrochloric acid (*Hinsberg, Schwantz*, Ber. **36**, 4040):



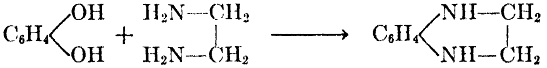
$$C_6H_4\left\langle\begin{array}{l}NH_2\\ NH_2\end{array}\right. + \begin{array}{l}CN\\ |\\ CN\end{array} \longrightarrow C_6H_4\left\langle\begin{array}{l}N{=}CNH_2\\ \qquad|\\ N{=}CNH_2\end{array}\right. \longrightarrow C_6H_4\left\langle\begin{array}{l}N{=}COH\\ \qquad|\\ N{=}COH\end{array}\right.$$

5. Condensation of *o*-nitrosophenols with acetaldehyde and ammonia or primary amines gives *dihydroquinoxalinols*, or *dihydroquinoxalones* (*Lange*, Ber. **42**, 574; Ger. Pats. 196563, 1906; 229127, 1909):



$$C_{10}H_6\left\langle\begin{array}{l}NO\\ OH\end{array}\right. + NH_2R + \begin{array}{l}CH_3\\ |\\ CHO\end{array} \longrightarrow C_{10}H_6\left\langle\begin{array}{l}NH{-}CH_2\\ \qquad\;\;|\\ NR{-}CO\end{array}\right.$$

6. *Tetrahydroquinoxalines* are obtained by condensation of dihydroxybenzenes with alkylenediamines:



$$C_6H_4\left\langle\begin{array}{l}OH\\ OH\end{array}\right. + \begin{array}{l}H_2N{-}CH_2\\ \qquad\;\;|\\ H_2N{-}CH_2\end{array} \longrightarrow C_6H_4\left\langle\begin{array}{l}NH{-}CH_2\\ \qquad\;\;|\\ NH{-}CH_2\end{array}\right.$$

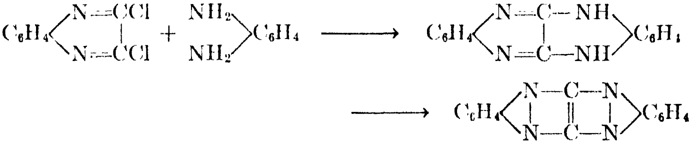
Behavior.—The quinoxalines are weak monoacid bases with an odor like quinoline or piperidine, soluble in alcohol and ether, less soluble in hot water than in cold. With $KMnO_4$ they are broken down to pyrazine-*o*-carboxylic acids (p. 298); when reduced they are usually converted to hydroquinoxalines (*Hinsberg, König*, Ber. **27**, 2181).

QUINOXALINE, m.p. 27°, b.p. 229° (*Chattaway, Humphrey*, J. **1929**, 645), is prepared from *o*-phenylenediamine with glyoxal bisulfite in aqueous solution at 60°; it is soluble in water, alcohol, and ether. Methyl iodide addition product, m.p. 175° (dec.). 6-**Methylquinoxaline, toluquinoxaline**, $CH_3C_6H_3(N_2C_2H_2)$, b.p. 245°, similarly from *o*-toluenediamine. 2,3-**Dimethylquinoxaline**, m.p. 106°, and 2,3,6-**trimethylquinoxaline**, m.p. 54°, b.p. 270°, from phenylene- or toluenediamine with biacetyl. 2-**Isopropylquinoxaline**, b.p. 270°, by condensation of *o*-phenylenediamine with γ-bromo-α,α-dimethylacetoacetic ester and subsequent heating with hydrochloric acid (*Conrad, Hock*, Ber. **32**, 1209). 2-**Phenylquinoxaline**, m.p. 78°, is formed by condensation of *o*-phenylenediamine with isonitrosoacetophenone and also by decomposition of benzo[*a*]phenazine (p. 305) (*Fischer, Schindler*, Ber. **39**, 2238). 2-**Phenyl- and** 3-**phenylbenzo**[*f*]**-quinoxaline**, m.p. 153° and 163°, are similarly obtained from isonitrosoacetophenone and 1,2-naphthalenediamine, and also by decomposition of dibenzo-

[*a,j*]phenazine and dibenzo[*a,h*]phenazine (*Fischer, Römer,* Ber. **41,** 2350). **2,3-Diphenylquinoxaline,** m.p. 124° (*Hinsberg, König,* Ber. **27,** 2181).

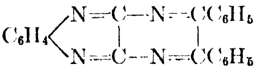
2-Quinoxalinol, m.p. 265°, from its carboxylic acid (see below). **2,*Bz*-Dimethyl-3-quinoxalinol,** 2-methyl-3-hydroxytoluquinoxaline, $CH_3C_6H_3[N_2C_2(CH_3)(OH)]$, m.p. 220°, and ***Bz*-methyl-2-phenyl-3-quinoxalinol,** $CH_3C_6H_3[N_2C_2(C_6H_5)(OH)]$, m.p. 196°, are prepared from toluenediamine with pyruvic acid and phenylglyoxylic acid; they are soluble in both acids and alkalis, colorless in the former, yellow in the latter.

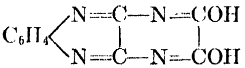
2,3-Quinoxalinediol, *phenyleneoxamide,* m.p. 410°, from *o*-phenylenediamine and oxalic acid or from 2,3-diaminoquinoxaline with hydrochloric acid, is converted by PCl_5 to **2,3-dichloroquinoxaline,** m.p. 150°. When warmed with *o*-phenylenediamine, the latter yields a condensation product which gives yellow solutions with a strong yellow-green fluorescence, and which is therefore called **fluoflavin;** this 5,11-dihydroquinoxalo[2,3-*b*]quinoxaline, $C_6H_4:(N_4C_2H_2):C_6H_4$ (I), m.p. 360°, oxidizes to **quinoxalo[2,3-*b*]quinoxaline** (II) (*Hinsberg, Pollak,* Ber. **29,** 784):

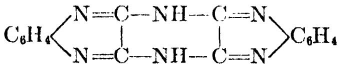

(I)

(II)

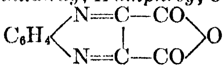
2,3-Diaminoquinoxaline, m.p. over 280°, from *o*-phenylenediamine and dicyanogen gas in methanol solution (p. 301), itself condenses with *o*-diketones, such as benzil and phenanthrenequinone, with pyruvic acid, and with oxalic acid, forming *polycyclic nuclei;* with 2,3-dichloroquinoxaline it yields 6,13-**dihydropyrazino**[2,3-*b*, 5,6-*b′*]**diquinoxaline, fluorubine** (*Hinsberg, Schwants,* Ber. **36,** 4039):



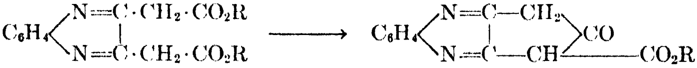




2,3-Benzoquinoxalinediol, *naphthaleneoxamide,* $C_{10}H_6(N_2C_2O_2H_2)$ (*Meyer, Müller,* Ber. **30,** 772; *Hinsberg, Schwants,* Ber. **36,** 4044).

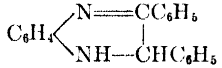
2,3-Quinoxalinedicarboxylic acid ($+2\,H_2O$), m.p. 190° (dec.) (anhydrous), from dihydroxytartaric acid with *o*-phenylenediamine (*Chattaway, Humphrey,* J. **1929,** 645), diethyl ester m.p. 83°, forms an *anhydride,*  $C_6H_4\left<\begin{matrix}N{=}C{-}CO\\ |\\ N{=}C{-}CO\end{matrix}\right>O$, m.p. 251°. The quinoxalinedicarboxamic acid obtained from the latter with NH_3 can be converted into **2-aminoquinoxaline-3-carboxylic acid** with bromine and aqueous sodium hydroxide (*Philips,* Ber. **28,** 1657). **2-Hydroxyquinoxaline-3-carboxylic acid,** m.p. 265° (dec.), from alloxan and *o*-phenylenediamine, by condensation and subsequent oxidation of the ureide first formed (*Hinsberg,* Ann. **292,** 248).

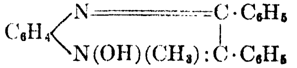
2,3-Quinoxalinediacetic ester, $C_8H_4N_2(CH_2CO_2C_2H_5)$, m.p. 58°, from *o*-phenylenediamine and ketipic acid ester, is condensed by sodium ethylate to 2-*oxo-2,3-dihydro-1-cyclopenta*[*b*]*quinoxaline-1-carboxylic acid ester* (*Thomas-Mamert, Striebel,* Bull. [3] **25,** 712).



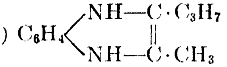
HYDROQUINOXALINES. 1,2-Dihydroquinoxalines are characterized by intensive yellow-green fluorescence. **1,2-Dihydro-2,3-diphenylquinoxaline** (I), **m.p. 146°, is formed by reduction of diphenylquinoxaline with stannous chloride, or from benzoin with** *o***-phenylenediamine** (***Fischer, Busch,*** **Ber. 24, 1870;** ***Hins-***

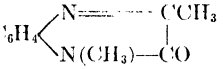
berg, König, Ber. **27**, 2182). **1-Methyl-2,3-diphenyl-1,2-dihydroquinoxaline** (*Kehrmann, Messinger,* Ber. **25**, 1632) can be oxidized to *1-methyl-2,3-diphenylquinoxalinium hydroxide* (II) (*cf.* p. 300).

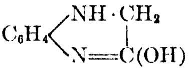
(I)

$$C_6H_4\left\langle\begin{array}{l}N{=\!=}CC_6H_5\\ \quad\;\;|\\ NH{-}CHC_6H_5\end{array}\right.$$


$$C_6H_4\left\langle\begin{array}{l}N{=\!=\!=\!=\!=}C\cdot C_6H_5\\ \qquad\qquad\quad\;|\\ N(OH)(CH_3):C\cdot C_6H_5\end{array}\right.$$
(II)

1,4-Dihydro-2-methyl-3-isopropylquinoxaline (III), colorless flakes, m.p. 124°, by condensation of *o*-phenylenediamine with mesityl oxide; dinitroso compound, m.p. 177° (*Ekeley,* Ber. **39**, 1646).

(III)

$$C_6H_4\left\langle\begin{array}{l}NH{-}C\cdot C_3H_7\\ \qquad\;\;\|\\ NH{-}C\cdot CH_3\end{array}\right.$$

(IV)

$$C_6H_4\left\langle\begin{array}{l}N{=\!=\!=}CCH_3\\ \qquad\quad\;|\\ N(CH_3){-}CO\end{array}\right.$$

(V)

$$C_6H_4\left\langle\begin{array}{l}NH\cdot CH_2\\ \qquad\;|\\ N{=\!=}C(OH)\end{array}\right.$$

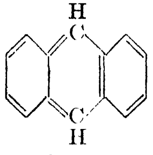
1,3-Dimethyl-2(1)-quinoxalone (IV), m.p. 78°, b.p. 308°, is obtained by condensation of methyl-*o*-phenylenediamine with pyruvic acid (*Kehrmann, Messinger,* Ber. **25**, 1630).

2-Hydroxy-3,4-dihydroquinoxaline (V), m.p. 132°, from *o*-phenylenediamine with monochloroacetic acid, is oxidized by chromic acid to quinoxalinediol (p. 302) (*Motylewski,* Ber. **41**, 800). **Dihydrobenzo[*f*]quinoxalinol**, m.p. 246°, from 1-nitroso-2-naphthol, acetaldehyde and ammonia (*cf.* p. 301).

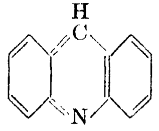
1,2,3,4-Tetrahydroquinoxaline, m.p. 97°, b.p. 289°, is prepared from pyrocatechol with ethylenediamine (*Ris,* Ber. **21**, 378) or by saponification of its 1,4-dibenzenesulfonyl derivative, $C_6H_4(NSO_2C_6H_5)_2(CH_2)_2$, the product of the reaction of 1,2-dibromoethane with dibenzenesulfonyl-*o*-phenylenediamine (*Hinsberg, Strupler,* Ann. **287**, 220).

2,3-Diphenyltetrahydroquinoxaline is obtained in two isomeric modifications, m.p. 105° and 142°, by reduction of diphenylquinoxaline with Na and alcohol (*Hinsberg, König,* Ber. **27**, 2184). The compound melting at 105° is the *racemic* form; it can be resolved into optically active antipodes with camphorsulfonic acid (*Bennett, Gibson,* J. **123**, 1570). The dimethyl compound has analogous stereochemical properties (*Gibson,* J. **1927**, 342).

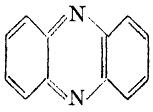
(3) **PHENAZINES,** *dibenzopyrazines.* The constitution of phenazine is similar to that of anthracene and of acridine:



Anthracene

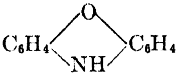


Acridine

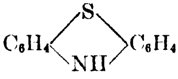


Phenazine

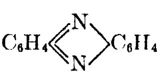
In preparation and properties it is more closely related to the dibenzo derivatives of 1,4-oxazine and 1,4-thiazine (pp. 275, 278):



Dibenzo-1,4-oxazine,
Phenoxazine



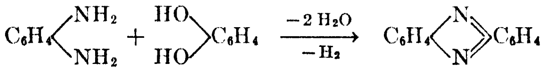
Dibenzo-1,4-thiazine,
Phenothiazine



Dibenzo-1,4-diazine,
Phenazine

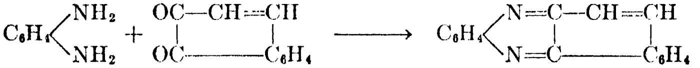
Like phenoxazine and phenothiazine, phenazine is the parent substance of a large number of dyes, some of which are technically important. Among these are the eurhodines, toluylene red, the indulines and safranine; some are derived from phenazine itself, some from benzophenazines, and some from dibenzophenazines. Several dyes occurring in nature (especially the products of the metabolism of fungi) have been found to be derivatives of phenazine (see pyocyanine, p. 313; chlororaphine, p. 309).

Methods of Preparation.—(*1*) By condensation of *o*-diamines with *o*-dihydroxybenzenes with elimination of water and hydrogen:



$$C_6H_4\Big\langle\begin{matrix}NH_2\\NH_2\end{matrix} + \begin{matrix}HO\\HO\end{matrix}\Big\rangle C_6H_4 \xrightarrow[-H_2]{-2\,H_2O} C_6H_4\Big\langle\begin{matrix}N\\N\end{matrix}\Big\rangle C_6H_4$$

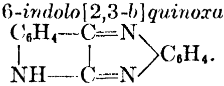
(*2*) From *o*-diamines with *o*-quinones, such as *o*-quinone, 1,2-naphthoquinone, phenanthrenequinone, croconic acid:



$$C_6H_4\Big\langle\begin{matrix}NH_2\\NH_2\end{matrix} + \begin{matrix}OC—CH{=}CH\\ |\qquad\quad |\\ OC———C_6H_4\end{matrix} \longrightarrow C_6H_4\Big\langle\begin{matrix}N{=}C—CH{=}CH\\ |\qquad\quad |\\ N{=}C———C_6H_4\end{matrix}$$

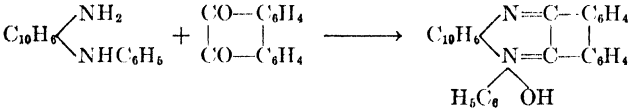
1,2-Naphthoquinone Benzo[*a*]phenazine

Isatin and *o*-phenylenediamine give 6-*indolo*[2,3-*b*]*quinoxaline, indophenazine* (*Schunck, Marchlewski*, Ber. **29**, 200):



$$\begin{matrix}C_6H_4—C{=}N\\ |\qquad\ |\\ NH—C{=}N\end{matrix}\Big\rangle C_6H_4.$$

However, azinium-bases result from the condensation of monosubstituted *o*-diamines with *o*-quinones (*cf.* quinoxalines, p. 300):

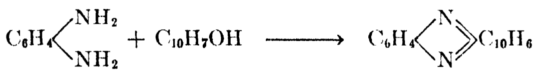


$$C_{10}H_6\Big\langle\begin{matrix}NH_2\\NHC_6H_5\end{matrix} + \begin{matrix}CO—C_6H_4\\ |\qquad |\\ CO—C_6H_4\end{matrix} \longrightarrow C_{10}H_6\Big\langle\begin{matrix}N{=}C—C_6H_4\\ |\qquad |\\ N{=}C—C_6H_4\end{matrix}\ \ \begin{matrix}\\ H_5C_6\ \ OH\end{matrix}$$

Phenyltribenzo[*a,c,h*]phenazinium hydroxide

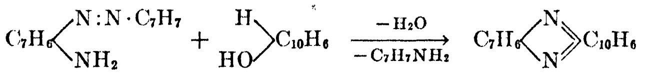
The same type of azinium compounds are formed from the azines with alkyl iodides and by deamination of induline and safranine bases (p. 310).

(*3*) Benzophenazines are obtained by oxidation of a mixture of an *o*-diamine with 1-naphthol:



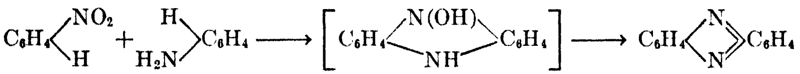
$$C_6H_4\Big\langle\begin{matrix}NH_2\\NH_2\end{matrix} + C_{10}H_7OH \longrightarrow C_6H_4\Big\langle\begin{matrix}N\\N\end{matrix}\Big\rangle C_{10}H_6$$

(*4*) Benzophenazines and dibenzophenazines are formed by fusion of *o*-aminoazo compounds with 2-naphthol (*Ullmann, Ankersmit*, Ber. **38**, 1811):



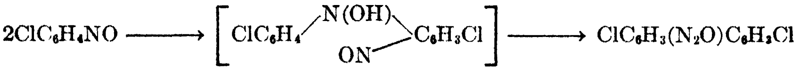
$$C_7H_6\Big\langle\begin{matrix}N{:}N\cdot C_7H_7\\NH_2\end{matrix} + \begin{matrix}H\\HO\end{matrix}\Big\rangle C_{10}H_6 \xrightarrow[-C_7H_7NH_2]{-H_2O} C_7H_6\Big\langle\begin{matrix}N\\N\end{matrix}\Big\rangle C_{10}H_6$$

(*5*) When heated with dry KOH, aromatic nitro derivatives and aromatic primary amines yield either phenazine oxides or phenazines, according to the temperature. This synthesis depends on the rearrangement of the nitro compound to a nitrosophenol under the influence of the alkali; the nitrosophenol then reacts with the amine (*Wohl, Aue*, Ber. **34**, 2442):



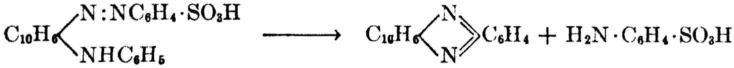
$$C_6H_4\Big\langle\begin{matrix}NO_2\\H\end{matrix} + \begin{matrix}H\\H_2N\end{matrix}\Big\rangle C_6H_4 \longrightarrow \left[C_6H_4\Big\langle\begin{matrix}N(OH)\\NH\end{matrix}\Big\rangle C_6H_4\right] \longrightarrow C_6H_4\Big\langle\begin{matrix}N\\N\end{matrix}\Big\rangle C_6H_4$$

(*6*) Phenazine oxides are produced by the action of concentrated H_2SO_4 on *para*-substituted nitrosobenzenes (when the *para*-position is unsubstituted, *p*-nitrosodiphenylhydroxylamines are formed: *Bamberger, Ham*, Ann. **382**, 82; *van Duin*, Rec. **38**, 89):

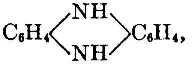


$$2ClC_6H_4NO \longrightarrow \left[ClC_6H_4\Big\langle\begin{matrix}N(OH)\\ON\end{matrix}\Big\rangle C_6H_3Cl\right] \longrightarrow ClC_6H_3(N_2O)C_6H_3Cl$$

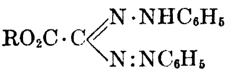
(*7*) Azines are prepared by fission of *o*-anilino- (toluido-, *etc.*) azo compounds. *o*-Anilinonaphthylazobenzenesulfonic acid, obtained by coupling naphthylphenylamine with diazobenzenesulfonic acid, decomposes when boiled with dilute acids into benzophenazine and sulfanilic acid:



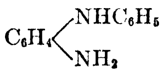
$$C_{10}H_6{<}^{N:NC_6H_4\cdot SO_3H}_{NHC_6H_5} \longrightarrow C_{10}H_6{<}^{N}_{N}{>}C_6H_4 + H_2N\cdot C_6H_4\cdot SO_3H$$

Behavior.—The phenazines are yellowish, weakly basic substances, which distill undecomposed. They are precipitated from their solutions in concentrated acids by addition of water. With alkyl iodides they form azinium iodides (*cf.* p. 309). Phenazines are converted by reduction to colorless, unstable dihydro derivatives, such as dihydrophenazine,  $C_6H_4{<}^{NH}_{NH}{>}C_6H_4$, which are readily oxidized back to the phenazines; highly colored compounds of the quinhydrone type are formed as intermediate products.

PHENAZINE, m.p. 171°, bright yellow needles, was first prepared: (*1*) by distillation of calcium azobenzoate, and was mistaken for *benzo*[*c*]*cinnoline*, azodiphenylene (*cf.* p. 287), with which it is isomeric; (*2*) also from *o*-phenylenediamine and pyrocatechol or *o*-quinone (*Kehrmann, Mermod,* Helv. **10,** 62) (see above); (*3*) from aminophenazine (p. 308) by deamination; (*4*) from aniline vapor by passage through an incandescent tube; (*5*) from formazylcarboxylic acid ester (I) by digestion with concentrated acids (*Bamberger, Wheelwright,* Ber. **25,** 3205); (*6*) from aminodiphenylamine (II) by oxidation, together with

(I) 

$$RO_2C\cdot C{<}^{N\cdot NHC_6H_5}_{N:NC_6H_5}$$

 (II)

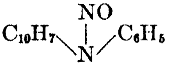
$$C_6H_4{<}^{NHC_6H_5}_{NH_2}$$

several other products (*Fischer, Heiler,* Ber. **26,** 383); and (*7*) from nitrobenzene, aniline, and KOH, a reaction which can also produce phenazine oxide, $C_6H_4(N_2O)C_6H_4$, m.p. 266°, which is reduced quantitatively to phenazine by stannous chloride (*Wohl, Aue,* Ber. **34,** 2446). In the laboratory it is best prepared by distillation of a mixture of 2-aminodiphenylamine with 2-nitrodiphenylamine and anhydrous sodium acetate (*Kehrmann, Havas,* Ber. **46,** 342), or by reduction of 2,2′-dinitrodiphenylamine with stannous chloride and hydrochloric acid in glacial acetic acid solution (*Eckert, Steiner,* Mo. **35,** 1153). Picrate, m.p. 181°. Phenazine is reduced by ammonium sulfide to **dihydrophenazine,** m.p. 212° (*Kehrmann, Havas,* Ber. **46,** 350; *Scholl,* Mo. **39,** 238); for the reduction in acid solution, see *Hinsberg, Garfunkel,* Ann. **292,** 260.

1-Methylphenazine, m.p. 108° (*McCombie, Scarborough, Waters,* J. **1928,** 353). **2-Methylphenazine,** m.p. 117° (*Kehrmann, Mermod,* Helv. **10,** 62).

2,6-Dimethylphenazine, m.p. 162°, is prepared by reduction of the dimethylphenazine oxide, m.p. 205°, which is obtained from *p*-nitrosotoluene by method *6* (see above).

Toluphenazine, m.p. 117°, from *o*-toluenediamine and pyrocatechol, or from *o*-aminophenyltolylamine with lead oxide (*Fischer,* Ber. **29,** 1873). **Benzo**[*a*]**phenazine,** *α,β-naphthophenazine,* m.p. 142° (*Kehrmann, Mermod,* Helv. **10,** 62), is formed by the general methods (p. 304) and also from naphthylphenylnitrosamine:



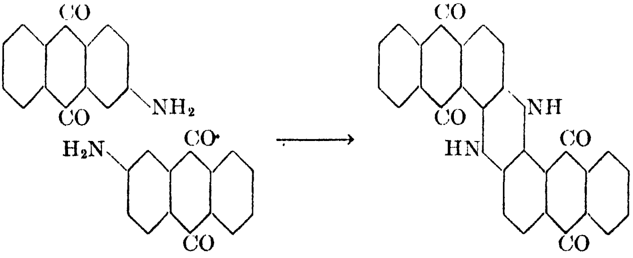
$$C_{10}H_7\diagdown\overset{NO}{\underset{N}{|}}\diagup C_6H_5$$

as acridine is obtained from formyldiphenylamine (*cf.* p. 257). It can be decomposed by oxidation to phenylquinoxaline (p. 301) (*Fischer, Schindler,* Ber. **39,** 2238). **Dibenzo**[*a,j*]**phenazine,** *s-α,β-naphthazine,* m.p. 243°, from 2,2′-dinaphthylnitrosamine (*Fischer, Junk,* Ber. **26,** 185) or from benzeneazo-2-naphthylamine by fusion with 2-naphthol (*Ullmann, Ankersmit,* Ber. **38,** 1816). **Dibenzo**[*a,h*]**phenazine,** *as-α,β-naphthazine,* m.p. 283° (*loc. cit.*), was first prepared from nitronaphthalene by heating to redness with lime ("naphthase," *Laurent,* 1840), and was therefore for a long time thought to be azonaphthalene.

It is also formed from 1,2-naphthalenediamine with 1,2-naphthoquinone; it is best prepared by condensation of nitroso-2-naphthylamine with 1-naphthylamine (*Fischer*, *Albert*, Ber. **29**, 2086) or by fusion of 2-naphthylamine with caustic alkalis, with or without the addition of oxidizing agents (Ger. Pat. 165226, 1904). By oxidative decomposition dibenzo[*a,j*]phenazine is converted to 2-phenylbenzo-[*f*]quinoxaline, and dibenzo[*a,h*]phenazine, to 3-phenylbenzo[*f*]quinoxaline (p. 301) (*Fischer*, *Schindler*, Ber. **41**, 390). **Dibenzo[*a,c*]phenazine,** *phenanthrophenazine*, $C_{14}H_8{:}N_2{:}C_6H_4$, m.p. 217°, from phenanthrenequinone and *o*-phenylenediamine. **Acenaphtho[1,2-*b*]quinoxaline,** *acenaphthophenazine*, $C_{12}H_6{:}N_2{:}C_6H_4$, m.p. 234°, from acenaphthenequinone and *o*-phenylenediamine [*Ampola*, *Recchi*, Atti accad. Lincei [5] **8** (1899), 209].

Anthrazine, *dinaphtho*[2,3-*a*; 2′,3′-*h*]*phenazine*, $C_{14}H_8\left\langle\begin{matrix}N\\ N\end{matrix}\right\rangle C_{14}H_8$, brown-red needles, m.p. about 390°, sublimable, is formed by the fusion of 2-anthramine with caustic alkalis (Ger. Pat. 172684, 1905); it is also obtained from indanthrene by distillation with zinc dust.

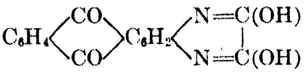
INDANTHRENE, *dihydroanthraquinoneazine*, 6,15-*dihydrodinaphtho*[2,3-*a*; 2′,3′-*h*]*phenazine*-5,18,9,14-*tetrone*, was technically prepared in the year 1901 by *R. Bohn* (Ber. **36**, 1258). The clarification of its structure is due mostly to the work of *R. Scholl* (Ber. **36**, 3410, 3427). The first indanthrene dyes were characterized by a high degree of light- and washfastness. Today the term "indanthrene" in technical vat dyestuff names indicates that the dye possesses these same properties, although the dyes so named are not necessarily derivatives of indanthrene. Indanthrene is prepared by fusion of 2-aminoanthraquinone with KOH at 205°:



2-Aminoanthraquinone Indanthrene

The following syntheses of indanthrene are of no technical importance, but are of value in determining its constitution: (*1*) by condensation of 1,2-aminoanthraquinone with 1,2-anthracenedione, followed by oxidation and reduction (Ger. Pat. 170562, 1904); (*2*) from 1-aminoanthraquinone by heating with dilute acids under pressure (Ger. Pat. 186636, 1906); (*3*) by condensation of 1-amino-2-bromo(chloro-)anthraquinone with itself (Ger. Pat. 158287, 1903). Indanthrene is an indigo-blue powder, very sparingly soluble in all organic solvents (solubility in quinoline, 1:500; in nitrobenzene, 1:5000); it crystallizes from quinoline in coppery needles. When heated with benzoyl chloride it forms a dibenzoyl derivative, red needles (*Scholl*, *Edlbacher*, Ber. **44**, 1732).

Indanthrene is oxidized by chromic acid or nitric acid to the yellow-green anthraquinoneazine, anthrazinetetrone, $C_{14}H_6O_2(N_2)C_{14}H_6O_2$, which can be reduced very readily to the dihydroazine. This stability of indanthrene, in contrast to the instability of other dihydrophenazines (p. 305), is analogous to the stability of fluorubine (p. 302), *etc.* By very energetic oxidation with chromic acid (40 hours' digestion), indanthrene is converted to 2,3-dihydroxynaphtho[2,3-*f*]-quinoxaline-7,12-dione:



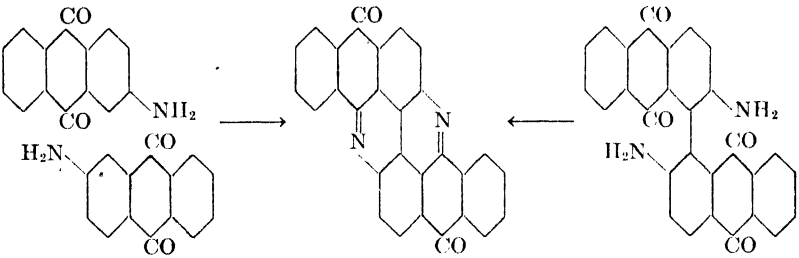
$$C_6H_4\left\langle\begin{matrix}CO\\ CO\end{matrix}\right\rangle C_6H_2\left\langle\begin{matrix}N{=}C(OH)\\ |\\ N{=}C(OH)\end{matrix}\right.$$

(*Scholl*, *Edlbacher*, Ber. **44**, 1727). The very unusual stability of indanthrene to oxidizing agents is due to the presence of negative radicals (the four carbonyl groups), an effect which has many counterparts (*Scholl*, Ber. **36**, 3422). The deep color of indanthrene is caused by interaction of the two quinone chromophore groups with the two NH-groups, which intensify the color; the latter factor is missing in the brightly colored anthraquinoneazines.

When reduced with hydrosulfite or zinc dust, indanthrene adds either 2 (blue vat) or 4 (brown vat) H-atoms, forming alkali-soluble products having a hydroquinone-like structure; these regenerate the insoluble dyestuff when exposed to the air. The vat dyeing with indanthrene is based on these reactions (*Scholl*, Ber. **36**, 3410; *Scholl, Steinkopf, Kabacznik*, Ber. **40**, 390).

A number of halogenated indanthrenes are technically important as dyes. They are oxidized to the corresponding azines with greater difficulty than in the case of indanthrene (*cf. Bohn*, Ber. **43**, 1000).

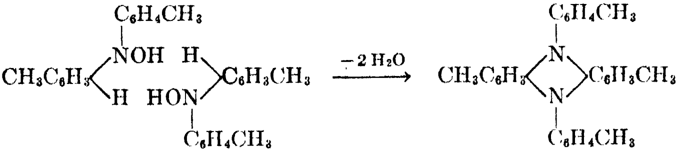
A heterocyclic compound closely related to indanthrene in properties and preparation is the yellow dye **flavanthrene**, 5,13-diazapyranthrene-8,16-dione (see formula below). Although it is not a 1,4-diazine, flavanthrene will be described here because of its similarity to indanthrene. Like indanthrene, it is formed by alkaline fusion of 2-aminoanthraquinone, but at higher temperatures (350°); a better method is digestion with antimony pentachloride in nitrobenzene solution. Its constitution is evident from its synthesis from 2,2'-dimethyl-1,1'-dianthraquinoyl (Vol. III, p. 667). It can be oxidized to the corresponding dianthraquinonyldicarboxylic acid, whose diamide is converted by bromine and alkali to 2,2'-diamino-1,1'-dianthraquinoyl; the latter condenses spontaneously with loss of 2 H_2O to flavanthrene (*Scholl*, Ber. **40**, 1691; *cf. Benesch*, Ber. **32**, 447). For other syntheses of flavanthrene, see *Scholl, Dischendorfer*, Ber. **51**, 452).



2-Aminoanthraquinone Flavanthrene 2,2'-Diamino-1,1'-dianthraquinoyl

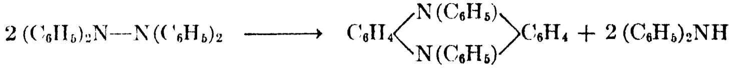
Flavanthrene is a yellow, very sparingly soluble powder, which crystallizes from quinoline in shiny brown-yellow needles. With alkaline hydrosulfite solution it gives a dark blue vat, from which cotton is dyed a very fast yellow by oxidation of the original blue shades in the air. When reduced energetically with HI and phosphorus, or when heated with zinc dust, flavanthrene is converted to **flavanthrine**, 5,13-*dihydro*-5,13-*diazapyranthrene*, $C_{28}H_{16}N_2$, brown needles, m.p. 390° (*Scholl*, Ber. **41**, 2304; *Scholl, Neovius*, Ber. **41**, 2534).

5,10-Diaryldihydrophenazines are obtained by the action of acids on diarylhydroxylamines:



Diarylhydroxylamines occur as intermediate products in the formation of diaryldihydrophenazines from tetraarylhydrazines and tetraaryltetrazones with concentrated acids (*Wieland*, Ber. **41**, 3478, 3498; *Wieland, Roseeu*, Ber. **45**, 496).

5,10-Diphenyldihydrophenazine, colorless needles, m.p. 172–175°, is formed together with diphenylamine when tetraphenylhydrazine is boiled in toluene solution; a primary fission of the tetraphenylhydrazine between the two N-atoms must be assumed, as in the spontaneous dissociation of hexaphenylethane into triphenylmethyl (*Wieland*, Ann. **381**, 202):

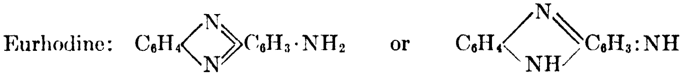


$$2\,(C_6H_5)_2N{-}N(C_6H_5)_2 \longrightarrow C_6H_4\!\left\langle\begin{matrix}N(C_6H_5)\\N(C_6H_5)\end{matrix}\right\rangle\!C_6H_4 + 2\,(C_6H_5)_2NH$$

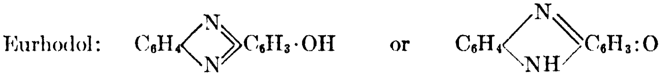
The colorless solution of diphenyldihydrophenazine in concentrated H_2SO_4 turns a deep dark blue on the addition of oxidizing agents.

Octahydrophenazine, picrate m.p. 168° (*Godchot*, C.r. **180**, 444).

Dyes are formed by the introduction of the auxochromic groups OH or NH_2 into the chromophoric phenazine. These amino- and hydroxyphenazines (eurhodines and eurhodols) may exist in either the normal form or a *para*-quinoid form (*Kehrmann*, Ann. **290**, 260), *e.g.*:



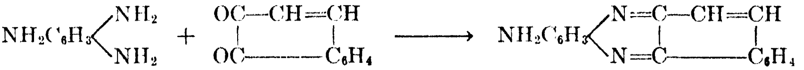
Eurhodine: $C_6H_4\!\left\langle\begin{matrix}N\\N\end{matrix}\right\rangle\!C_6H_3{\cdot}NH_2$ or $C_6H_4\!\left\langle\begin{matrix}N\\NH\end{matrix}\right\rangle\!C_6H_3{:}NH$



Eurhodol: $C_6H_4\!\left\langle\begin{matrix}N\\N\end{matrix}\right\rangle\!C_6H_3{\cdot}OH$ or $C_6H_4\!\left\langle\begin{matrix}N\\NH\end{matrix}\right\rangle\!C_6H_3{:}O$

Derivatives of these compounds phenylated on the ring nitrogen, the safranines and indulines, are more valuable as dyes than the simpler derivatives. They are discussed as azinium compounds on pp. 309 *ff*.

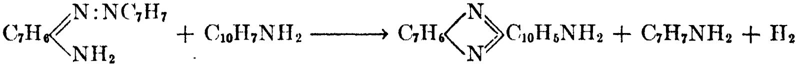
AMINOPHENAZINES. (*1*) **Monoaminophenazines,** *eurhodines*, are prepared: (*a*) Like the parent compounds, from aminated *o*-diamines with quinones:



$$NH_2C_6H_3\!\left\langle\begin{matrix}NH_2\\NH_2\end{matrix}\right. + \begin{matrix}OC{-}CH{=}CH\\ |\qquad\quad |\\ OC{-}{-}{-}C_6H_4\end{matrix} \longrightarrow NH_2C_6H_3\!\left\langle\begin{matrix}N{=}C{-}CH{=}CH\\ |\qquad\quad |\\ N{=}C{-}{-}{-}C_6H_4\end{matrix}\right.$$

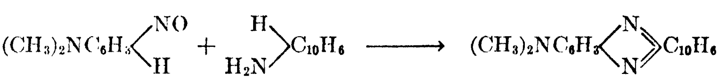
Triaminobenzene 1,2-Naphthoquinone Aminobenzo[*a*]phenazine

(*b*) By the action of aromatic monoamines on *o*-aminoazo compounds:



$$C_7H_6\!\left\langle\begin{matrix}N{:}NC_7H_7\\NH_2\end{matrix}\right. + C_{10}H_7NH_2 \longrightarrow C_7H_6\!\left\langle\begin{matrix}N\\N\end{matrix}\right\rangle\!C_{10}H_5NH_2 + C_7H_7NH_2 + H_2$$

(*c*) By condensation of *N*-dichloroquinonimines or *p*-nitrosodimethylaniline with monoamines in which the *p*-position is occupied (if it is free, indamines are formed):



$$(CH_3)_2NC_6H_3\!\left\langle\begin{matrix}NO\\H\end{matrix}\right. + \left.\begin{matrix}H\\H_2N\end{matrix}\right\rangle\!C_{10}H_6 \longrightarrow (CH_3)_2NC_6H_3\!\left\langle\begin{matrix}N\\N\end{matrix}\right\rangle\!C_{10}H_6$$

The eurhodines are weak bases; their salts are scarlet. When diluted, the red solutions in concentrated H_2SO_4 turn black, green, and finally red, a phenomenon caused by the gradual dissociation of salts stable only in the presence of concentrated acids. The solutions in ether have a yellow-green fluorescence. When heated with acids the aminophenazines are converted to phenazinols, eurhodols (see below).

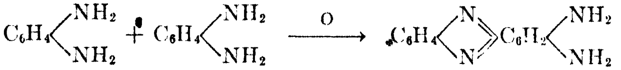
1-Aminophenazine, m.p. 172°, red flakes (*Kehrmann, Prunier*, Helv. **7**, 984).

2-Aminophenazine, m.p. 290°, red needles, has been prepared from diaminophenazine by heating with zinc dust, from diaminodiphenylamine, $NH_2[2]C_6H_4$-$NHC_6H_4[3]NH_2$, by oxidation (*Fischer*, Ber. **29**, 1874), and from *o*-nitraniline by condensation with aniline in the presence of zinc chloride (*Wohl, Lange*, Ber. **43**, 2186).

Aminobenzophenazine, $C_{10}H_6N_2C_6H_3NH_2$, m.p. 267°, from chrysoidine and 2-

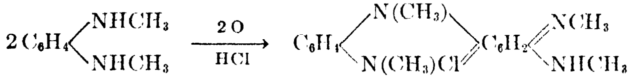
naphthol or from 2-naphthylamine and *N*,*N*-dichloroquinonimine (*Wedekind*, Ber. **38**, 1844).

(*2*) **Unsymmetrical diaminophenazines** are obtained by oxidation of *o*-diamines (together with aminophenazinols: *Ullmann*, *Mauthner*, Ber. **36**, 4026):

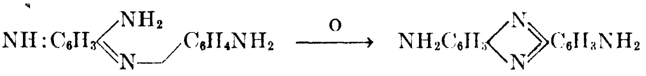


2,3-Diaminophenazine

When dialkylated *o*-diamines are oxidized, *p*-quinoid azonium salts are formed (*Fischer*, Ber. **37**, 552):



(*3*) **Symmetrical diaminophenazines, toluylene red group.** *s*-Diaminophenazines are prepared by oxidation of aminated indamines:



s-Diaminophenazine

In place of the indamines, a mixture of a *p*-diamine with a *m*-diamine can be oxidized; the same products are obtained when N-chloroquinonimines are reacted with *m*-diamines. **Toluylene red, dimethyldiaminotoluphenazine,** NH_2-$C_7H_5N_2C_6H_3N(CH_3)_2$, is formed by the oxidation of *p*-aminodimethylaniline with *m*-toluylenediamine, with intermediate formation of toluylene blue (Vol. III, p. 248). Toluylene red, orange-red needles, dyes silk and mordanted cotton scarlet; it is marketed under the name *neutral red*. The monoacid salts are red; the di- and triacid salts, stable only in the presence of concentrated acids, are blue to green. When deaminated it gives dimethylaminotoluphenazine.

PHENAZINECARBOXYLIC ACIDS. **1-Phenazinecarboxylic acid**, m.p. 239°, has been synthesized by application of method *5* (p. 304) to anthranilic acid (*Kögl*, *Postowsky*, Ann. **480**, 293). The amide, m.p. 241°, is identical with the *hydroxychlororaphine* obtained from the fungoid dye *chlororaphine* by treatment with oxygen (*Kögl*, *Postowsky*, Ann. **480**, 280).

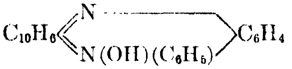
PHENAZINOLS, *eurhodols*, are prepared: (*1*) from the aminophenazines by heating with concentrated hydrochloric acid at 180°; (*2*) synthetically, by condensation of *o*-diamines with hydroxylated *o*-quinones (*Kehrmann*, *Stanoyévitch*, Helv. **8**, 661). The phenazinols resemble the aminophenazines in color and fluorescence.

1-Phenazinol (*hemipyocyanine*), m.p. 158°, is obtained through its methyl ether, m.p. 168°, formed by the condensation of *o*-phenylenediamine with the monomethyl ether of pyrogallol (*Wrede*, *Strack*, Ber. **62**, 2051; Z.physiol.Chem. **177**, 185). It is also produced by the cleavage of *pyocyanine* (p. 313) by alkali in the presence of air (*Wrede*, *Strack*, Z.physiol.Chem. **181**, 60). **α-Benzophenazinol,** $HOC_{10}H_5N_2C_6H_4$, prepared from aminobenzophenazine or by condensation of hydroxy-1,2-naphthaquinone with *o*-phenylenediamine, forms two isomeric methyl ethers, an oxygen ether and a nitrogen ether, which correspond to the two forms given above for eurhodol (p. 308) (*Kehrmann*, *Messinger*, Ber. **24**, 2167).

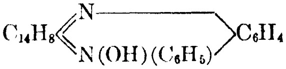
Di- and polyhydroxyphenazines are obtained by methods similar to those used for the monohydroxy derivative. Condensation of *o*-phenylenediamine with dihydroxydihydronaphthalenedione yields benzophenazine oxide, $(C_6H_4N_2C_{10}H_6)O$, a compound of the ethylene oxide type, which is rearranged by hydrochloric acid to α-benzophenazinol, $C_6H_4N_2C_{10}H_5OH$, m.p. 198° (*Zincke*, Ber. **26**, 617; *Zincke*, *Wiegand*, Ann. **286**, 61).

HALOGENO PHENAZINES are prepared from the corresponding phenazinols with phosphorus halides. The 3-chloro- and 3,6-dichlorophenazinium chlorides from indone chloride (p. 313) and safraninone chloride (p. 315) have been investigated in detail.

AZINIUM COMPOUNDS. These compounds are important because they are the parent compounds of the induline and safranine dyes, from which they are obtained by diazotization in strongly acid solution and to which they are usually converted by treatment with ammonia or alkalis. The ease with which the azinium compounds are substituted, by other radicals, such as the desoxybenzoin residue (*Sachs*, Ber. **31**, 3073), as well as by OH-, NH_2-, and amine groups, is also characteristic of the azoxonium and azothionium compounds (pp. 275, 279); it is found to some degree in all quinones. In view of this, certain regularities in the substitution of asymmetric azinium compounds are more satisfactorily explained by *ortho*-quinoid formulas (*Kehrmann*, Ber. **33**, 395) such as the following:

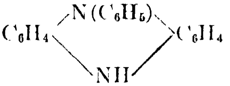


$$C_{10}H_6\left\langle\begin{matrix}N\\N(OH)(C_6H_5)\end{matrix}\right\rangle C_6H_4$$



$$C_{14}H_8\left\langle\begin{matrix}N\\N(OH)(C_6H_5)\end{matrix}\right\rangle C_6H_4$$

For the synthesis of phenazinium compounds, see p. 304. The phenazinium salts are generally isolated by means of their ferric chloride double salts. **Ethylphenazinium iodide,** $C_6H_4(N_2C_2H_5\cdot I)C_6H_4$ and **methylbenzophenazinium iodide,** $C_{10}H_6(N_2CH_3\cdot I)C_6H_4$, are formed from the corresponding azines with alkyl iodides (*Fischer, Hepp*, Ber. **30**, 391). **Phenylphenazinium chloride,** from aposafranine chloride by deamination, ferric chloride double salt, $C_6H_4(N_2C_6H_5\cdot Cl)C_6H_4\cdot FeCl_3$, m.p. 186°, is reduced by stannous chloride to **5-phenyl-5,10-dihydrophenazine:**

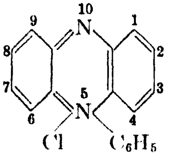


$$C_6H_4\left\langle\begin{matrix}N(C_6H_5)\\NH\end{matrix}\right\rangle C_6H_4$$

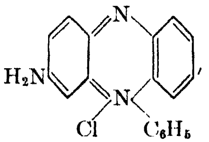
m.p. 143°, the true analogue of phenoxazine and phenothiazine (*Kehrmann*, Ann. **322**, 69). **Phenylbenzophenazinium chloride,** $C_{10}H_6(N_2C_6H_5\cdot Cl)C_6H_4$, from rosinduline and isorosinduline (p. 312). An isomeric **phenylbenzophenazinium chloride** has been obtained from *ψ*-rosinduline, and also by condensation of 1,2-naphthoquinone and phenylphenylenediamine (*Kehrmann*, Ber. **29**, 2316; *Kehrmann, Schaposchnikoff*, Ber. **29**, 2967; *Kehrmann, Helwig*, Ber. **30**, 2629). **Phenyldibenzophenazinium chloride,** $C_{10}H_6(N_2C_6H_5\cdot Cl)C_{10}H_6$, from naphthinduline (*Kehrmann, Sutherst*, Ber. **32**, 939). **Phenyldibenzo**[*a,c*]**phenazinium chloride,** *flavinduline*, $C_{14}H_8(N_2C_6H_5Cl)C_6H_4$, from phenanthrenequinone and *o*-aminodiphenylamine [*Hinsberg, Garfunkel*, Ann. **292**, 266; Ger. Pat. 97639, 1897; *Kikina*, J.Russ.Phys.Chem.Soc. **32** (1900), 170]. For the products of the reaction of flavinduline with organomagnesium compounds, see *Freund, Richard*, Ber. **42**, 1104. **Phenylacenaphtho**[1,2-*b*]**phenazinium nitrate,** $C_{12}H_6(N_2C_6H_5NO_3)C_6H_4$, from acenaphthenequinone and *o*-aminodiphenylamine (*Ullmann, Cassirer*, Ber. **43**, 441).

Aposafranines, Aposafranones, Safranines, Safranones, Indulines[*]

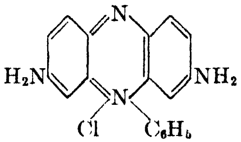
These important groups of dyes, which have been known for a long time (*Caro, Dale*, 1865; *Griess, Martius*, 1866), are amino and hydroxy derivatives of N-phenylphenazinium salts:



5-Phenylphenazinium chloride



3-Amino-5-phenylphenazinium chloride. Aposafranine chloride



3,7-Diamino-5-phenylphenazinium chloride. Safranine chloride

These structures are proven experimentally by the conversion of aposafranine chloride to phenylphenazinium chloride by diazotization and removal of the diazo group.

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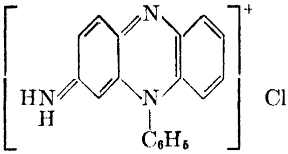
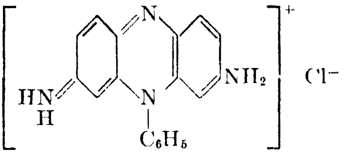
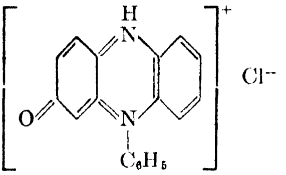
[*] For the numerous patents covering these dyes, see Frdl., Vols. **I–XX**.

As in the case of the phenoxazinium and phenothiazinium dyes, these compounds also (at least in the form of their monoacid salts) are better represented by a *para*-quinoid structure, than by the *ortho*-quinoid formulas (p. 310); in solution a desmotropic equilibrium between the two forms appears to exist (*cf. Kehrmann,* Ann. **414,** 142). The spectroscopic data on these systems confirm the above conclusions (*Kehrmann,* Ber. **47,** 1895; Ann. **414,** 131). According to the *p*-quinoid formulas, the dyes are the hydrochlorides of 3-phenazime and 7-amino-3-phenazime:

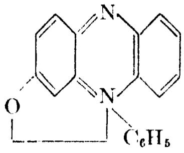

Aposafranine chloride


Safranine chloride

The corresponding oxygen-compounds, the aposafranones and safranones, which are derived from 3-phenazinone [this compound must not be confused with the dibenzopyridazine (p. 287), nor with antipyrine, which are both sometimes called phenazone] have analogous formulas:


Aposafranone chloride

Also, for the free base:

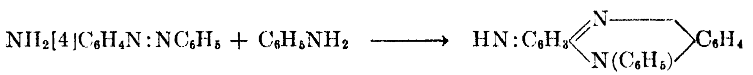

Phenolbetaine formula

For the free phenazinone base the phenolbetaine formula is also used.

In the *p*-quinoid form the phenazine dyes may be regarded as indamines or indophenols to which a further nitrogen atom has been added to close the phenazine ring (*cf.* the analogous relation of the dyes of the phenoxazine or phenothiazine series).

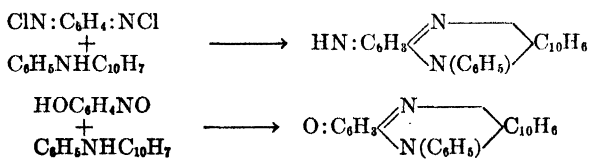
The indulines, which are derived from the same basic nucleus (phenazime), contain phenyl nuclei in the amino groups, and are therefore aniline derivatives of phenazime. The term induline, however, does not always have the same connotation.

Aposafranines are obtained: (*a*) by heating *p*-aminoazo compounds with monoamines in the presence of some mineral acid:



$$\mathrm{NH_2[4]C_6H_4N{:}NC_6H_5 + C_6H_5NH_2 \longrightarrow HN{:}C_6H_3{<}\begin{matrix}N\text{———}\\N(C_6H_5)\end{matrix}{>}C_6H_4}$$

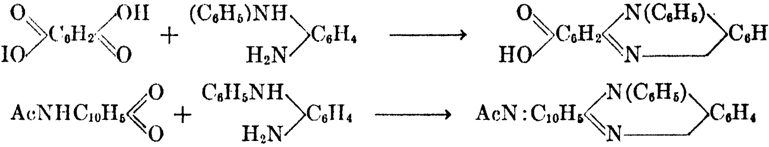
The intermediate and side-products are *p*-quinonediimines, such as quinonedianil, anilinoquinonedianil, dianilinoquinonedianil, or azophenine [*Fischer, Hepp,* Ber. **25,** 2731; Z.Farb.Textilchemie **1** (1902), 457]. This reaction is therefore related to the formation of benzophenazimes and phenazinones (isorosindulines and isorosindones) from N,N′-dichloroquinonimine, *p*-nitrosoanilines, and *p*-nitrosophenols with alkyl- or aryl-2-naphthylamines (*Fischer, Hepp,* Ber. **29,** 2753; *Fischer,* Ber. **34,** 940):



$$\mathrm{\begin{matrix}ClN{:}C_6H_4{:}NCl\\+\\C_6H_5NHC_{10}H_7\end{matrix} \longrightarrow HN{:}C_6H_3{<}\begin{matrix}N\text{———}\\N(C_6H_5)\end{matrix}{>}C_{10}H_6}$$

$$\mathrm{\begin{matrix}HOC_6H_4NO\\+\\C_6H_5NHC_{10}H_7\end{matrix} \longrightarrow O{:}C_6H_3{<}\begin{matrix}N\text{———}\\N(C_6H_5)\end{matrix}{>}C_{10}H_6}$$

(*b*) Phenazinones and phenazimes are also formed by condensation of hydroxyquinones and aminoquinones with phenylated *o*-diamines (*Kehrmann*, Ber. **28**, 1714; Ann. **290**, 262):



The dyes technically known as indulines can be divided into four classes:

(*1*) **Benzindulines,** $HN:C_6H_3(N_2C_6H_5)C_6H_4$, from phenazime.
(*2a*) **Isorosindulines,** $HN:C_6H_3(N_2C_6H_5)C_{10}H_6$ }, from benzophenazime.
(*2b*) **Rosindulines,** $HN:C_{10}H_5(N_2C_6H_5)C_6H_4$ }
(*3*) **Naphthindulines,** $HN:C_{10}H_5(N_2C_6H_5)C_{10}H_6$, from dibenzophenazime.
(*4*) **Flavindulines** (p. 310), from dibenzo[*a,c*]phenazime and tribenzo[*a,c,h*]-phenazime.

The *ms*-alkyl derivatives, corresponding to these *ms*-phenyl derivatives have also been prepared by various methods (*cf. Fischer, Hepp*, Ber. **30**, 294).

The benzindulines and isorosindulines have similar properties, both being derivatives of benzoquinone, while the rosindulines resemble the naphthindulines, which are also derived from naphthoquinone. The former of the two groups forms sparingly soluble, violet to blue salts; their application in calico printing depends on their solubility in acetin (acetin-printing). The rosindulines and naphthindulines are stronger bases. Their salts are deep red, with red fluorescence. Their solutions in strong acid show the same color changes on dilution that the safranines do. When warmed with anilines, the indulines, like the quinones, give aniline derivatives; the indones, when warmed with alkali, yield hydroxyindones. For the action of ammonia on indulines, see the safranines.

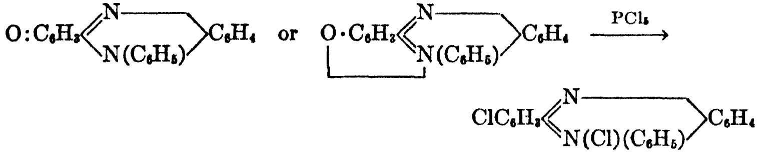
Aposafranine, benzinduline, is formed by the deamination of phenosafranine (p. 314) or isophenosafranine (p. 314; *Kehrmann*, Ann. **322**, 69) and is converted by further deamination to phenylphenazinium salts, which regenerate aposafranine when treated with ammonia. When warmed with aniline, aposafranine yields **anilinoaposafranine** (*Kehrmann*, Ber. **28**, 1709; *Kehrmann, Schaposchnikoff*, Ber. **29**, 2967). Aposafranine is obtained together with several other induline derivatives from *p*-aminoazobenzene and aniline [*cf. Fischer, Hepp*, Ber. **33**, 1498; Z.Farb.Textilchemie **1** (1902), 457; *Barbier, Sisley*, Sitzungsber. kgl.preuss.Akad.Wiss. **1907**, 440). If *p*-aminoazobenzene is heated with *p*-phenylenediamine, a mixture of aminated indulines is produced; this is used as a cotton dye under the name *paraphenylene blue* (*cf. Fischer, Hepp*, Ann. **286**, 195).

Isorosinduline, $C_{10}H_6(N_2C_6H_5)C_6H_3NH$, from N,N′-dichloroquinonimine and phenyl-2-naphthylamine, yields phenylbenzophenazinium salts when deaminated (*Fischer, Hepp*, Ber. **29**, 2753). The dimethyl derivative of isorosinduline is prepared from *p*-nitrosodimethylaniline with aniline and 1-naphthylamine; an anilino derivative of this compound is the well-known *Basle blue* (*Fischer, Hepp*, Ann. **272**, 311).

Rosinduline, $HNC_{10}H_5(N_2C_6H_5)C_6H_4$, m.p. 199 °, is obtained from benzeneazo-1-naphthylamine with aniline, from *o*-hydroxy-1,4-naphthoquinonimine with *o*-aminodiphenylamine and, together with the isomeric **ψ-rosinduline,** from 4-acetamido-1,2-naphthoquinone with phenyl-*o*-phenylenediamine. ψ-Rosinduline differs from rosinduline in the position of the NC_6H_5-group in the naphthalene ring (*Kehrmann, Messinger*, Ber. **24**, 2167; *Kehrmann*, Ann. **290**, 262). Like isorosinduline, rosinduline may be deaminated to phenylbenzophenazinium salts, from which rosinduline may be regenerated by the action of ammonia. A series of isomeric rosindulines have been prepared by various methods (*cf. Kehrmann, Levy*, Ber. **31**, 3097; *Kehrmann, Filatoff*, Ber. **32**, 2627; *Kehrmann, Wolff*, Ber. **33**, 1543; *Kehrmann*, Helv. **8**, 655). **Phenylrosinduline,** m.p. 235 °; *azocarmine* is its disulfonic acid (Ger. Pat. 45370, 1888, Frdl. **II**, 202).

Naphthinduline, $HNC_{10}H_5(N_2C_6H_5)C_{10}H_6$, m.p. 250 °, is obtained from benzeneazo-1-naphthylamine with naphthylamine and aniline (*Fischer, Hepp*, Ann. **262,** 262; **272,** 311). *Naphthyl violet* is its anilino derivative. *Naphthyl blue*, the anilino derivative of phenylnaphthinduline, is formed by inner condensation of benzeneazo-1-naphthylphenylamine.

INDONES (*Fischer, Hepp*, Ann. **286,** 242). The indones are derivatives of phenazinone. Since they form *chlorophenazinium chlorides* with PCl_5, a phenolbetaine structure must be considered for these compounds together with the *p*-quinone formula (p. 311) (*Fischer, Hepp*, Ber. **33,** 1485; *Kehrmann, Stern*, Ber. **41,** 12):

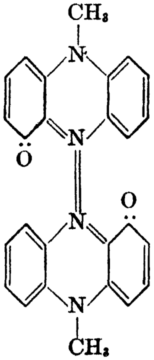


$$O{:}C_6H_3\left<\begin{matrix}N\\N(C_6H_5)\end{matrix}\right>C_6H_4 \text{ or } O\cdot C_6H_3\left<\begin{matrix}N\\N(C_6H_5)\end{matrix}\right>C_6H_4 \xrightarrow{PCl_5} ClC_6H_3\left<\begin{matrix}N\\N(Cl)(C_6H_5)\end{matrix}\right>C_6H_4$$

The indones add dimethyl sulfate to give methyl sulfate salts of methoxyphenazinium hydroxides (*Kehrmann*, Ann. **322,** 73).

Aposafranone, *benzindone*, $C_{18}H_{12}N_2O$, m.p. 242°, prepared from aposafranine bromide with aqueous sodium hydroxide (*Fischer, Hepp*, Ber. **33,** 1487), reacts with PCl_5 to form *phenylchlorophenazinium chloride* (see above), and with hydroxylamine to form *aminoaposafranone*, $C_{18}H_{11}N_2O(NH_2)$ (*Fischer, Hepp*, Ber. **38,** 3435). **Rosindone,** $OC_{10}H_5(N_2C_6H_5)C_6H_4$, m.p. 259°, is used technically in the form of its sulfonic acid as a ponceau-red dye. With PCl_5 it gives phenylchlorobenzophenazinium chloride, which is converted by KSH to *thiorosindone*; with dimethyl sulfate, rosindone gives N-*methyl*-N′-*phenylmethoxybenzophenazinium sulfate*, $CH_3OC_{10}H_5(C_6H_5N_2\cdot OSO_3CH_3)C_6H_5$. For the oxidation of rosindone to *rosindonic acid* with CrO_3, see *Fischer*, Ber. **36,** 3622. **Isorosindone,** $C_{10}H_6(N_2C_6H_5)C_6H_3O$, m.p. 224°, from nitrosophenol and phenyl-2-naphthylamine (*Fischer, Hepp*, Ber. **29,** 2755), is converted by PCl_5 to phenylbenzochlorophenazinium chloride (*Fischer, Hepp*, Ber. **33,** 1494), and, by hydroxylamine, to aminoisorosindone (*Fischer, Römer*, Ber. **40,** 3406). **Naphthindone,** $C_{10}H_5O$-$(N_2\cdot C_6H_5)C_{10}H_6$, m.p. 295°, reacts with PCl_5 to form phenylchlorodibenzophenazinium chloride (*Fischer, Hepp*, Ber. **33,** 1497).

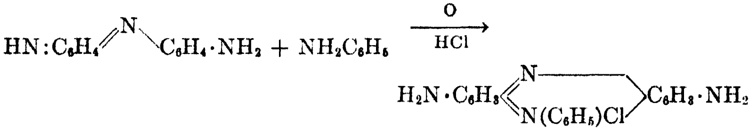
Pyocyanine, $C_{26}H_{20}N_4O_2$, has been found to be a derivative of 2-*phenazinone*. This blue dye is a product of the metabolism of *Bacillus pyocyaneus*. *Wrede* (Z.physiol.Chem. **181,** 64) assigns it this constitution:



With alkali in the presence of oxygen, 1-hydroxyphenazine (hemipyocyanine) (p. 309) is formed. For the synthesis of this dye, see *Wrede, Strack*, Z.physiol. Chem. **181,** 74.

SAFRANINES. The safranine salts may be considered as symmetric diamino derivatives of azinium salts (*Nietzki*, Ber. **29,** 1442). They are prepared:

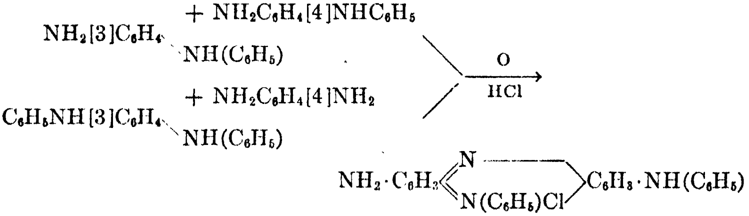
(*1*) By oxidation of a mixture of an indamine and a monoamine (*cf. Hardin,* Ber. **33,** 1212):



Phenylene blue Phenosafranine chloride

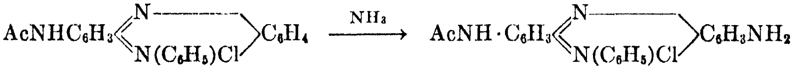
The mechanism of this reaction must be quite similar to that given for methylene blue (p. 280).

(*2*) By oxidation of a mixture of *m*-amino derivatives of diphenylamine with *p*-diamines or dichloroquinonimines (*Jaubert,* Ber. **28,** 1579; *Nietzki,* Ber. **29,** 1444):



Phenomauveine

(*3*) By the action of ammonia or amines on the acetyl derivatives of indulines:



The safranines form stable monoacid salts, usually red. Their solutions in concentrated sulfuric acid or hydrochloric acid are green; when diluted, they turn blue, then red (due to dissociation of unstable polyacid salts; *cf.* monoaminophenazines, p. 308). These color changes are reversed by addition of acid to dilute solutions of the salts. The slight solubility of the nitrates is a characteristic property. The alcoholic solutions of the safranines show a strong yellow-red fluorescence. In contrast to the induline azinium bases (p. 311), the free azinium bases of the safranine series are stable in aqueous solution (*Hantzsch, Osswald,* Ber. **33,** 315). The safranines can be reduced to leuco bases, which regenerate the dyes very rapidly in the presence of alkali.

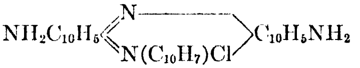
Phenosafranine chloride, $C_{18}H_{15}N_4Cl$, shiny green flakes or steel-blue needles, yields safranol (p. 315) when digested with barium hydroxide. When its monoazo derivative is boiled with alcohol, it is converted to aposafranine chloride (p. 311), whose acetyl derivative gives an acetylated phenosafranine on treatment with ammonia (*Kehrmann, Schaposchnikoff,* Ber. **30,** 1565). *as*-**Dimethyl**- and **diethylphenosafranine** (*Nietzki,* Ber. **28,** 1356) are obtained from dimethyl- and diethyl-*p*-phenylenediamine with 2 molar proportions of aniline. **Tetraethylphenosafranine** is the violet dye *amethyst.*

Isophenosafranine chloride, $(NH_2)_2C_6H_2(N_2C_6H_5Cl)C_6H_4$, differs from safranines in having both amino groups attached to one benzene nucleus. It is prepared from dinitrophenyldihydrophenazine, the condensation product of picric acid with *o*-aminodiphenylamine, by the same method used for the analogous compounds of the oxazine and thiazine series (pp. 272, 277) (*Kehrmann, Prunier,* Helv. **7,** 984; *Hoehn,* Helv. **8,** 275).

TOLUSAFRANINE, $C_{18}H_{13}(CH_3)_2N_4Cl$, is the principal constituent of the ordinary safranine which is used to produce scarlet and rose shades on cotton and silk. It is obtained from *p*-toluenediamine (see p. 314) with 1 mol *o*-toluidine and 1 mol aniline; technically this mixture of bases is produced from the "aniline oil for safranine," which is partially converted by diazotization to *p*-aminoazotoluene and then reduced to *p*-toluenediamine and *o*-toluidine.

Naphthophenosafranine chloride, $NH_2C_{10}H_5(N_2C_6H_5Cl)C_6H_3NH_2$; its acetyl derivative is formed from acetylisorosinduline with ammonia (*Kehrmann, Schaposchnikoff,* Ber. **30**, 1566).

Indazine, $C_6H_5NHC_6H_3(N_2ClC_6H_5)C_6H_3N(CH_3)_2$, m.p. 218°, is closely related to the safranines in its formation. It is prepared from diphenyl-*m*-phenylenediamine with nitrosodimethylaniline. The analogous nonmethylated compound, from nitrosoaniline and diphenyl-*m*-phenylenediamine, or from *m*- and *p*-aminodiphenylamine (see above) is identical with **phenomauveine,** which is akin to **mauveine,** the first aniline dye to be produced technically (*Perkin,* 1856). Mauveine is obtained by oxidation of aniline containing toluidine with bichromate or PbO_2 [*Cobenzl,* Österr.chem.Z. **28** (1925), 25]. Another member of the safranine group is **magdala red** (*Hofmann,* Ber. **2**, 412), which is formed from aminoazonaphthalene with 1-naphthylamine hydrochloride and apparently has this constitution:

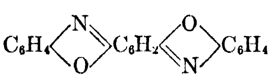


$$NH_2C_{10}H_5\left\langle\begin{matrix}N\text{———————}\\N(C_{10}H_7)Cl\end{matrix}\right\rangle C_{10}H_5NH_2$$

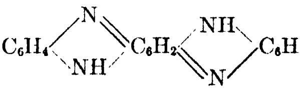
(*Fischer, Hepp,* Ber. **26**, 2235; *Kehrmann, Schaposchnikoff,* Ber. **30**, 1567).

SAFRANONES and **SAFRANOLS** are symmetric amino and hydroxy derivatives of aposafranone (p. 313); they are formed similarly to the safranines from *m*-hydroxydiphenylamines with nitrosodimethylaniline or nitrosophenol (*Jaubert,* Ber. **28**, 270, 1578; *Harries, Klamt,* Ber. **28**, 503; *Nietzki,* Ber. **28**, 1354). *Safranone,* $C_{18}H_{13}N_3O$, and *safranol,* $C_{18}H_{12}N_2O_2$, are also obtained by digesting phenylsafranine with barium hydroxide solution or KOH (*Fischer, Hepp,* Ber. **30**, 399). With PCl_5 safranol gives *dichlorophenazinium chloride,* $ClC_6H_3(N_2 \cdot ClC_6H_5)C_6H_3Cl$ (*Fischer, Hepp,* Ber. **31**, 301).

Fluorindines. The simplest member of this group of dyes, fluorindine, is the analogue of triphenodioxazine (p. 277);

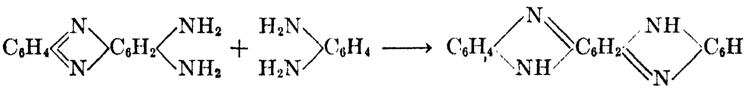


Triphenodioxazine



Fluorindine = 5,12-Dihydroquinoxalo[2,3-*b*] phenazine

As triphenodioxazines are formed by oxidation of *o*-aminophenols, so the fluorindines are prepared by oxidation or heating of salts of *o*-diamines, *as*-diaminophenazines (p. 309) being formed as intermediate products:

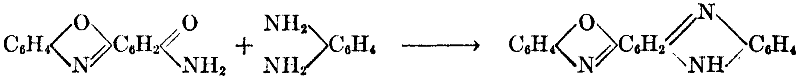


as-Diaminophenazine *o*-Phenylenediamine Fluorindine

The fluorindines are shiny green crystals, which sublime undecomposed and are very sparingly soluble. Their solutions show a beautiful brick-red fluorescence.

Methylfluorindine, $C_6H_4(N_2H)C_6H_2(N_2 \cdot CH_3)C_6H_4$, is obtained from diaminophenazine hydrochloride with methyl-*o*-phenylenediamine. **Phenylfluorindine,** $C_6H_4N_2HC_6H_2N_2(C_6H_5)C_6H_4$, has been prepared by condensation of aposafranine chloride (p. 311) with *o*-phenylenediamine (*Fischer, Hepp,* Ber. **29**, 367). **Diphenylfluorindine,** $C_6H_4(N_2C_6H_5)C_6H_2(N_2 \cdot C_6H_5)C_6H_4$, is formed by oxidation of azophenine (Vol. III, p. 247) or by sublimation of phenylinduline (see above) (*Fischer, Hepp,* Ber. **28**, 293). For dibenzo[*a,c*]fluorindine, phenanthrophenofluorindine, from *o*-diaminoflavinduline, see *Kehrmann,* Ber. **33**, 405.

12-Quinoxalo[2,3-*b*]phenoxazine, triphenazineoxazine, is a mixed oxazine-phenazine; it is prepared from *as*-dihydroxyphenazine with *o*-aminophenol or from aminophenoxazone with *o*-phenylenediamine (*Fischer, Hepp,* Ber. **28,** 299; *Diepolder,* Ber. **31,** 499; **34,** 2272; **35,** 2816):

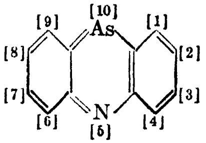


Higher condensed ring-systems have been obtained by this same method (*Kehrmann, Lozoz,* Helv. **10,** 339; *Kehrmann, Collaud,* Helv. **11,** 1028).

4. ARSAZINES

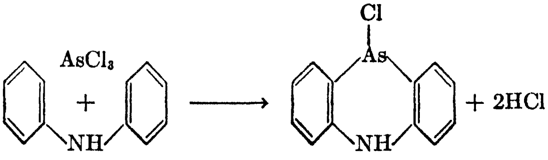
Phenarsazine is a tricyclic ring-system derived from the phenazine ring by replacement of an N-atom by As:

Phenarsazine



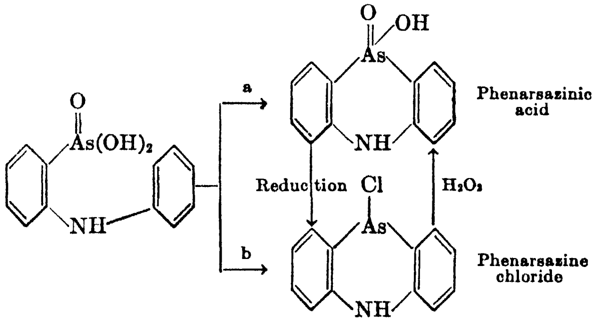
Derivatives of this ring-system may be obtained in two ways:

1. By heating diphenylamine and substituted diphenylamines with AsCl$_3$ (*Wieland, Rheinheimer,* Ann. **423,** 1):



10-Chloro-5,10-dihydrophenarsazine
= Phenarsazine chloride

2. From N-phenyl-*o*-arsanilic acid (*a*) by elimination of water by digesting with HCl, with formation of phenarsazinic acids; (*b*) by reduction with HCl, SO$_2$ in the presence of some iodine, with formation of 10-chloro-5,10-dihydrophenarsazine (*Gibson, Johnson,* J. **1927,** 2499; **1929,** 1229, 2743):



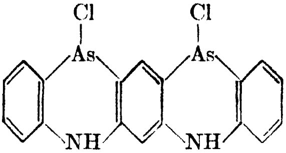
The phenarsazinic acids can be obtained from the 10-chloro-5,10-dihydrophenarsazines by oxidation with H$_2$O$_2$; this conversion can be reversed by reduction with SO$_2$ in alcoholic hydrochloric acid solution.

When phenarsazine derivatives are treated with bromine, the arsenic is split off, and brominated diphenylamines are produced (*Elson, Gibson, Johnson,* J.

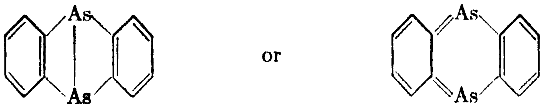
1929, 1080). With nitric acid nitro derivatives of phenarsazine are formed. **Phenarsazine**, m.p. about 310°, orange-red, prepared by heating the methyl ether obtained from 10-chloro-5,10-dihydrophenarsazine (*Wieland, Rheinheimer*, Ann. **423**, 16). Phenarsazine readily adds a number of compounds, such as HCl, alcohol, and acetic acid; the products are derivatives of dihydrophenarsazine.

10-Chloro-5,10-dihydrophenarsazine, m.p. 192°, by method *1* or *2* (*Wieland, Rheinheimer*, Ann. **423**, 12; *Burten, Gibson*, J. **1926**, 464). **10-Chloro-2-methyl-**, **10-chloro-3(1?)-methyl-**, **10-chloro-2,8-dimethyl-5,10-dihydrophenarsazine**, m.p. 200°, 216°, 262° (*Burton, Gibson*, J. **1926**, 464; *Gibson, Johnson*, J. **1929**, 767). **10-Chloro-5,10-dihydrophenarsazine-4-carboxylic acid**, m.p. 243°, from anthranilic acid according to method *2b*.

Application of method *2* to *o*-, *m*-, and *p*-phenylenediamine yields compounds containing two arsazine rings (*Gibson, Johnson*, J. **1928**, 2204):



The replacement of the second nitrogen atom in phenazine by As gives the compound:



Arsanthrene, m.p. about 340° (Diphenyldiarsine)

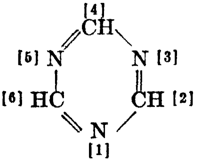
This orange-yellow compound has been prepared from the corresponding dichloride by reduction (*Kalb*, Ann. **423**, 68). *Arsanthrenic acid*, m.p. over 360°, corresponding to arsanthrene, is produced by oxidation of arsanthrene dichloride with HNO_3 (*Wieland, Rheinheimer*, Ann. **423**, 31).

III. SIX-MEMBERED RINGS WITH THREE HETERO ATOMS

1. TRIAZINES

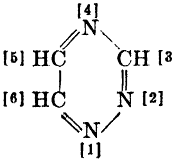
Derivatives of all three possible isomeric triazines are known:

(A)



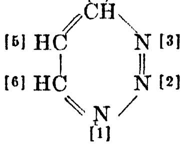
s-Triazine,
1,3,5-Triazine, Cyanidine

(B)



as-Triazine,
1,2,4-Triazine

(C)



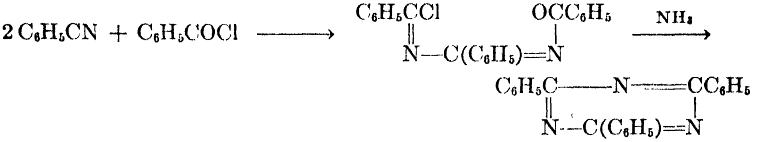
v-Triazine,
1,2,3-Triazine

(A) *s*-Triazines, Cyanidines

The formula of the symmetric triazine is the same as that of the hypothetical *trihydrocyanic acid*, to which certain metallohydrocyanic acids are referred (*cf. Pascal*, C.r. **180**, 1850). A number of polymeric cyano compounds, such as cyanuric acid, thiocyanuric acid, cyanuric chloride, melamine, and isomelamine, are derivatives of this triazine. They are treated in Vol. I.

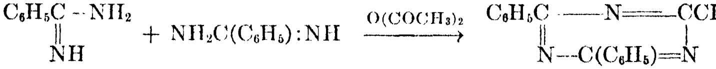
Alkyl- and phenyl-*s*-triazines are obtained:

1. By the action of aluminum chloride on a mixture of benzonitrile and benzoyl chloride or fatty acid chloride. When benzoyl chloride is used, the reaction, which is improved by the addition of ammonium chloride, apparently takes the following course (*Eitner*, *Krafft*, Ber. **25**, 2263):



$$2\,C_6H_5CN + C_6H_5COCl \longrightarrow \begin{array}{ll} C_6H_5CCl & OCC_6H_5 \\ \| & | \\ N\text{—}C(C_6H_5)\text{=}N & \end{array} \xrightarrow{NH_3} \begin{array}{ll} C_6H_5C\text{——}N\text{==}CC_6H_5 & \\ \| \qquad\qquad | & \\ N\text{—}C(C_6H_5)\text{=}N & \end{array}$$

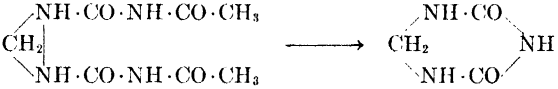
2. By the reaction of fatty acid anhydrides on aromatic carboxylic acid amidines (*Pinner*, Ber. **25**, 1624; *Rappeport*, Ber. **34**, 1989):



$$\begin{array}{l} C_6H_5C\text{—}NH_2 \\ \| \\ NH \end{array} + NH_2C(C_6H_5)\text{:}NH \xrightarrow{O(COCH_3)_2} \begin{array}{l} C_6H_5C\text{——}N\text{==}CCH_3 \\ \| \qquad\qquad | \\ N\text{—}C(C_6H_5)\text{=}N \end{array}$$

Carbonyl chloride reacts like the acid anhydrides, forming *s*-triazinols (*Pinner*, Ber. **25**, 1424).

Derivatives of hexahydro-*s*-triazine are formed by the action of mineral acids on *bis*-(acetylureido)-methanes (Ger. Pat. 479349, 1926, Frdl. **XVI**, 2909):



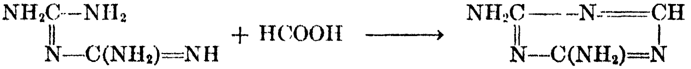
$$CH_2\left\langle\begin{array}{l} NH\cdot CO\cdot NH\cdot CO\cdot CH_3 \\ NH\cdot CO\cdot NH\cdot CO\cdot CH_3 \end{array}\right. \longrightarrow CH_2\left\langle\begin{array}{l} NH\cdot CO \\ NH\cdot CO \end{array}\right\rangle NH$$

The *s*-triazines are weak, monoacid bases; they can be decomposed more or less readily into NH_3 and carboxylic acids. They are important intermediates for various dyes (see Ger. Pats. 433100, 1924, Frdl. **XV**, 329; 441985, 1925, Frdl. **XV**, 558).

2,6-Diphenyl-4-methyl-*s*-triazine, m.p. 110°, from benzamidine and acetic anhydride, can be oxidized to diphenyltriazinecarboxylic acid, which yields on decarboxylation, **2,6-diphenyl-*s*-triazine**, m.p. 75° (*Kraft*, *Koenig*, Ber. **23**, 2382). **2,4,6-Triphenyl-*s*-triazine, cyaphenine**, was first prepared from benzoyl chloride and potassium cyanate (*Cloez*, 1859). It is also obtained by polymerization of benzonitrile with concentrated H_2SO_4, from benzonitrile, benzoyl chloride, and $AlCl_3$, and from a mixture of cyanuric chloride and bromobenzene by treatment with Na (proof of constitution; *cf.* also *Diels*, *Liebermann*, Ber. **36**, 3193). Nascent hydrogen splits it into NH_3 and lophine (p. 128). **Tri-(trichloromethyl)-*s*-triazine**, $C_3(CCl_3)_3N_3$, m.p. 96°, is formed by the polymerization of trichloroacetonitrile. **Tri-(α,α-dichloroethyl)-*s*-triazine**, $C_3(CCl_2\cdot CH_3)_3N_3$, m.p. 74°, from propionitrile with chlorine, gives with KSH trithioacetyl-*s*-triazine, $C_3(CS\cdot CH_3)_3N_3$ (*Troeger*, *Hornung*, J.pr. **57**, 357).

2,4-Diphenyl-6-*s*-triazinol, m.p. 289°, from benzylideneamidine with $COCl_2$ (*cf. Pinner*, Ber. **23**, 163), forms a crystalline sodium salt. With PCl_5 it gives diphenylchloro-*s*-triazine, m.p. 139°, which behaves like an acid chloride, *e.g.* it is readily converted by ammonia to 2,4-diphenyl-6-amino-*s*-triazine, m.p. 172°. **6-Methyl-2,4-*s*-triazinediol**, $C_3(CH_3)(OH)_2N_3$, from acetylurethan and urea (*Ostrogovich*, Ann. **288**, 318).

Amino-*s*-triazine, *aminohydrocyanuride*, $C_3H_2(NH_2)N_3$, and **diamino-*s*-triazine**, *diaminohydrocyanuride*, $C_3H(NH_2)_2N_3$, m.p. 235°, are formed from cyanuramide dichloride and cyanurodiamide monochloride by reduction. Diamino-*s*-triazine is identical with **formoguanamine** (*Diels*, Ber. **32**, 1219; *cf.* Vol. I, p. 531). Guanamines are produced by heating the guanidine salts of fatty acids alone or biguanide with fatty acids:



$$\begin{array}{l} NH_2C\text{—}NH_2 \\ \| \\ N\text{—}C(NH_2)\text{=}NH \end{array} + HCOOH \longrightarrow \begin{array}{l} NH_2C\text{——}N\text{==}CH \\ \| \qquad\qquad | \\ N\text{—}C(NH_2)\text{=}N \end{array}$$

Biguanide **Diamino-*s*-triazine, Formoguanamine**

Piperidylamino-*s*-triazine, $C_3(NC_5H_{10})(NH_2)HN_3$, m.p. 194°, is similarly obtained from piperidylbiguanide by heating with formic acid or by treatment with chloroform and KOH even at 0° (*Bamberger, Seeberger,* Ber. **25**, 525).

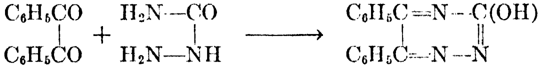
s-**Triazinetriol** is the normal cyanuric acid (Vol. I, p. 520), **trichloro-*s*-triazine** is cyanuric chloride (Vol. I, p. 523), **triamino-*s*-triazine** is melamine (Vol. I, p. 530) and **diamino-*s*-triazinol** and **amino-*s*-triazinediol** are ammelide and ammeline (Vol. I, p. 530).

When cyanuric chloride is treated with methanol or ethanol and zinc dust, the product is **dimethoxy-** or **diethoxychloro-*s*-triazine,** $C_3(OR)_2ClN_3$, m.p. 81° and m.p. 44°, b.p. 144° (13 mm.). Dimethoxychloro-*s*-triazine is converted by KSH to **dimethoxymercapto-*s*-triazole,** which is hydrolyzed by hydrochloric acid to **mercapto-*s*-triazinediol,** *monothiocyanuric acid,* $C_3(OH)_2(SH)N_3$, m.p. 316° (dec.) (*Diels, Liebermann,* Ber. **36**, 3191). The reaction products of cyanuric chloride with many classes of organic compounds, have been patented [*cf.* Swiss Pats. 103430; 106074-106119; 106385-9; 106394-8; 106400-2; 106405-10 (all 1923); and Brit. Pat. 220302, 1924].

Isocyanuric acid is 2,4,6(1,3,5)-*s*-**triazinetrione.**

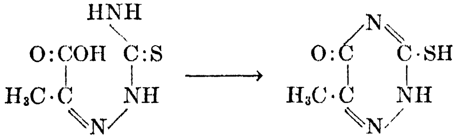
(B) *as*-Triazines, 1,2,4-Triazines

Only a few derivatives of the simple *as*-triazine ring are known. 5,6-**Diphenyl-3-*as*-triazinol,** m.p. 218°, results from the condensation of benzil with semicarbazide hydrochloride in glacial acetic acid (*Biltz,* Ann. **339**, 243):

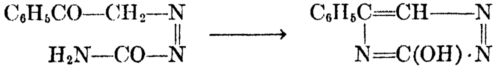


$$\begin{array}{l} C_6H_5CO \\ | \\ C_6H_5CO \end{array} + \begin{array}{l} H_2N-CO \\ \quad\quad | \\ H_2N-NH \end{array} \longrightarrow \begin{array}{l} C_6H_5C{=}N-C(OH) \\ \quad\quad | \quad\quad\quad \| \\ C_6H_5C{=}N-N \end{array}$$

5,6-**Diphenyl-3-amino-*as*-triazine,** $C_3(C_6H_5)_2(NH_2)N_3$, m.p. 175°, is prepared from benzil and aminoguanidine nitrate (*Thiele, Bihan,* Ann. **302**, 309). For other triazines obtained from aromatic diketones by the same method, see *De,* Quart.J.Indian Chem.Soc. **4** (1927), 183. The condensation also takes place with thiosemicarbazones of α-oxo carboxylic acids, leading to the formation of 3-mercapto-5(2)-*as*-triazones (*van Alphen,* Rec. **47**, 673):

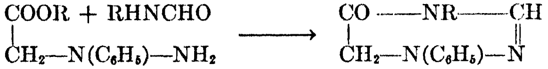


Several other *as*-triazines are obtainable from phenacylazocyanide, $C_6H_5CO{-}CH_2N{:}NCN$, whose amide, amide chloride, and thiamide are converted by elimination of water to **phenylhydroxy-, phenylchloro-,** and **phenylmercapto-*as*-triazine,** m.p. 234°, 123° and 200° (*Wolff, Lindenhayn,* Ber. **36**, 4126):



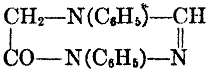
$$\begin{array}{l} C_6H_5CO-CH_2-N \\ \quad\quad\quad\quad\quad\quad\quad \| \\ H_2N-CO-N \end{array} \longrightarrow \begin{array}{l} C_6H_5C{=}CH-N \\ \quad\quad | \quad\quad\quad\quad \| \\ N{=}C(OH)\cdot N \end{array}$$

1-**Phenyl-** and 1-**phenyl-4-alkyl-1,6-dihydro-5(4)-*as*-triazones** are prepared by heating *as*-phenylhydrazinoacetic ester with formamide and substituted formamides (*Harries,* Ber. **28**, 1228):



$$\begin{array}{l} COOR + RHNCHO \\ | \\ CH_2-N(C_6H_5)-NH_2 \end{array} \longrightarrow \begin{array}{l} CO-NR-CH \\ | \quad\quad\quad\quad\quad\quad \| \\ CH_2-N(C_6H_5)-N \end{array}$$

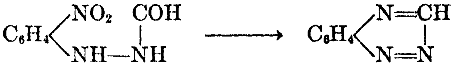
1,4-**Diphenyl-1,6-dihydro-5(4)-*as*-triazone,** m.p. 205° is so obtained with formanilide; an isomeric 1,4-**diphenyl-4,5-dihydro-6(1)-*as*-triazone,**



$$\begin{array}{l} CH_2-N(C_6H_5)-CH \\ | \quad\quad\quad\quad\quad\quad\quad \| \\ CO-N(C_6H_5)-N \end{array}$$

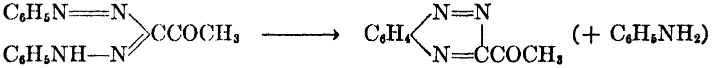
m.p. 174°, is formed from phenylglycine phenylhydrazide, $C_6H_5NHCH_2CON(C_6H_5)NH_2$, (Vol. III, p. 90) with anhydrous formic acid (*Widman*, Ber. **26**, 2616). **1,4-Diphenyl-2,3-dihydro-5,6(4,1)-*as*-triazinedione**, m.p. 258°, is prepared from *as*-phenylhydrazinoacetanilide with phosgene (*Rupe*, *Heberlein*, *Roesler*, Ann. **301**, 69). **6-Methyl-1,6-dihydro-3,5(2,4)-*as*-triazinedione**, m.p. 214°, from α-semicarbazidopropionitrile, $NH_2CONH \cdot NHCH(CH_3)CN$, with concd. hydrochloric acid, loses two hydrogen atoms when treated with bromine, forming **6-methyl-3,5-*as*-triazinediol**, m.p. 209° (*Thiele*, *Bailey*, Ann. **303**, 76).

A larger number of derivatives of **1,2,4-benzotriazine**, *α-phentriazine*, are known. They are prepared: (*1*) by reduction of *sym.* *o*-nitrophenylacylhydrazines:



$$C_6H_4\left\langle\begin{matrix}NO_2 & COH\\ & |\\ NH & -NH\end{matrix}\right. \longrightarrow C_6H_4\left\langle\begin{matrix}N= & CH\\ & |\\ N= & N\end{matrix}\right.$$

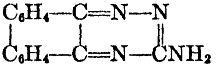
(*2*) By condensation of formazyl compounds by boiling with strong acids (*Bamberger*, *Wheelwright*, Ber. **25**, 3206; *Bamberger*, *Lorenzen*, Ber. **25**, 3540; *Bamberger*, *Witter*, Ber. **26**, 2788):



$$\left.\begin{matrix}C_6H_5N=\!=\!=N\\ C_6H_5NH-N\end{matrix}\right\rangle CCOCH_3 \longrightarrow C_6H_4\left\langle\begin{matrix}N= & N\\ & |\\ N= & CCOCH_3\end{matrix}\right. \quad (+\ C_6H_5NH_2)$$

The 1,2,4-benzotriazines are yellow, crystalline substances with an alkaloid-like odor. They are slightly basic.

1,2,4-Benzotriazine, $C_6H_4(CN_3H)$, m.p. 75°, b.p. 235–240°, is obtained from *o*-nitrophenylformylhydrazine by reduction, or from formazylcarboxylic acid ester by elimination of aniline and CO_2. **3-Methyl-1,2,4-benzotriazine**, $C_6H_4[CN_3(CH_3)]$, m.p. 89°, b.p. 250–255°, from *o*-nitrophenylacetylhydrazine. **3-Acetyl-1,2,4-benzotriazine**, $C_6H_4[CN_3(COCH_3)]$, m.p. 114°, from formazyl methyl ketone. **3-Aminophenanthro[9,10]-*as*-triazine**;



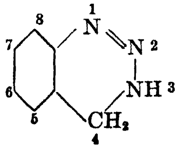
$$\begin{matrix}C_6H_4 & -C= & N- & N\\ | & | & & \|\\ C_6H_4 & -C= & N- & CNH_2\end{matrix}$$

m.p. 262°, and **3-phenanthro[9,10]-*as*-triazinol**, m.p. 285° (dec.), from phenanthrenequinone with aminoguanidine nitrate and semicarbazide hydrochloride (*Thiele*, *Bihan*, Ann. **302**, 310; *Schmidt*, *Schairer*, *Glatz*, Ber. **44**, 276).

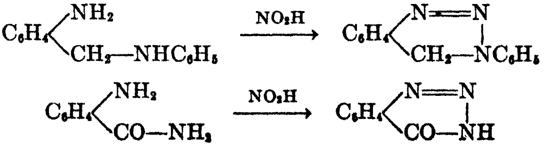
The products of the reaction of aldehydes with *o*-aminoazo compounds, which were first thought to be 2-phenyldihydro-1,2,4-benzotriazines, have been identified as N-phenylaminobenzimidazoles (*Fischer*, J.pr. **104**, 102; **107**, 16).

(C) *v*-Triazines

3,4-Dihydro-1,2,3-benzotriazines:



which may be considered ring-homologues of benzotriazole (p. 151), are prepared from *o*-aminobenzylamines and *o*-aminobenzamides with nitric acid, just as the dihydroquinazolines are obtained with carboxylic acids (p. 293):



$$C_6H_4\left\langle\begin{matrix}NH_2\\ CH_2-NHC_6H_5\end{matrix}\right. \xrightarrow{NO_2H} C_6H_4\left\langle\begin{matrix}N=\!=\!= & N\\ & |\\ CH_2- & NC_6H_5\end{matrix}\right.$$

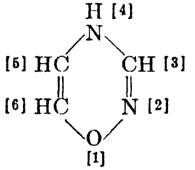
$$C_6H_4\left\langle\begin{matrix}NH_2\\ CO-NH_2\end{matrix}\right. \xrightarrow{NO_2H} C_6H_4\left\langle\begin{matrix}N=\!= & N\\ & |\\ CO- & NH\end{matrix}\right.$$

3-Phenyl-3,4-dihydro-1,2,3-benzotriazine, $C_6H_3[CH_2N_3(C_6H_5)]$, m.p. 128° (dec.) (*Busch*, Ber. **25**, 445). **3-Benzyl-3,4-dihydro-1,2,3-benzotriazine,** C_6H_4-$[CH_2N_3(C_7H_7)]$, m.p. 91° (*Busch*, J.pr. **51**, 257). 1,2,3-**Benzotriaz**-4(3)-**one, benzazimide,** $C_6H_4(CON_3H)$, m.p. 212° (dec.), from *o*-aminobenzamide with nitrous acid, is also obtained from 3-aminoindazole by oxidation with hydrogen peroxide in acid solution (*cf.* p. 116); its oxime is produced by the action of N_2O_3 on *o*-aminobenzylideneaminoxime (*Busch*, Ber. **25**, 445; *Zacharias*, J.pr. **43**, 446; *Finger*, Ber. **37**, 432; J.pr. **48**, 92; *Kratz*, J.pr. **53**, 210; *Pinnow*, *Sämann*, Ber. **29**, 626). 1,2,3-**Benzotriazine**-4(3)-**thione,** $C_6H_4(CSN_3H)$, m.p. 187°, from *o*-aminothiobenzamide with nitrous acid (*Reissert*, *Grube*, Ber. **42**, 3719). **3-Phenyl-1,2,3-benzotriaz**-4(3)-**one,** $C_6H_4(CON_3C_6H_5)$, m.p. 151°, from *o*-aminobenzanilide with N_2O_3 (*König*, *Reissert*, Ber. **32**, 784), is also formed when diazoaminobenzene-*o*-carboxylic acid ester is digested with alcohol (*Mehner*, J.pr. **64**, 70).

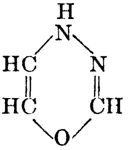
2. OXADIAZINES

Oxadiazines contain one oxygen atom and two nitrogen atoms in their ring. Only a few are known, and most of these have been prepared by reactions similar to those producing the corresponding five-membered rings, the oxadiazoles.

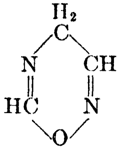
Derivatives of the following isomeric oxadiazines have been reported:



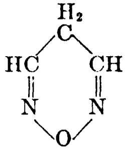
1,4,2-Oxadiazine



1,4,3-Oxadiazine

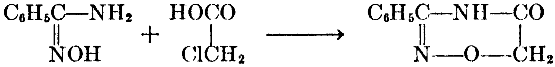


1,2,5,4-Oxadiazine



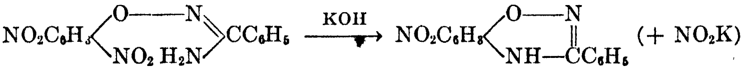
1,2,6,4-Oxadiazine

(a) 1,4,2-**OXADIAZINES.** As the five-membered 1,2,4-oxadiazoles are prepared from amidoximes with carboxylic acid chlorides, so their six-membered ring-homologues are formed from amidoximes with α-chloro-aliphatic acids (*Koch*, Ber. **22**, 3161; *Werner*, *Sonnenfeld*, Ber. **27**, 3353; *Werner*, *Bial*, Ber. **28**, 1374; *Werner*, *Falck*, Ber. **29**, 2656; *Wolf*, Ber. **31**, 2110):

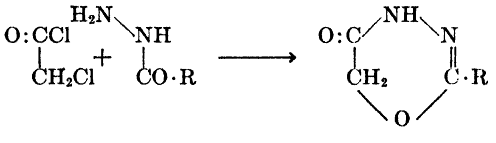


$$\begin{array}{lclcl} C_6H_5C{-}NH_2 & & HOCO & & C_6H_5C{-}NH{-}CO \\ \| & + & | & \longrightarrow & \|\qquad\qquad | \\ NOH & & ClCH_2 & & N{-}O{-}CH_2 \end{array}$$

Benzo derivatives of this ring are obtained from dinitrophenol ethers of amidoximes with alkali, one nitro group being eliminated (*Werner*, *Herberger*, Ber. **32**, 2686):

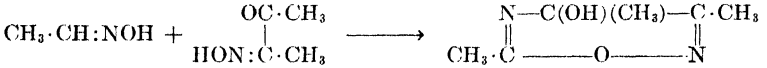


(b) Derivatives of 1,4,3-**OXADIAZINE** are produced by the action of chloroacetic acid chloride or its alkyl or aryl homologues on monoacylhydrazines (*van Alphen*, Rec. **47**, 909; **48**, 163, 417):



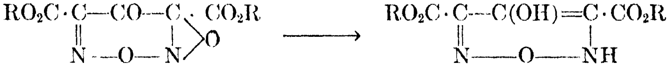
This method gives 1,4,3-oxadiazin-5(6)-ones; with oxalyl chloride, 5,6-diones are obtained (*van Alphen*, Rec. **47**, 673).

(c) The 1,2,5,4-**OXADIAZINES**, which are also ring-homologues of the oxadiazoles, are prepared by condensation of isonitroso ketones with aldoximes (*Diels, Sasse*, Ber. **40**, 4052):



3,4,6-Trimethyl-1,2,5,4-oxadiazinol-4

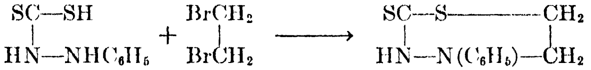
(d) The six-membered 1,2,6,4-**OXADIAZINES** correspond to the five-membered 1,2,5-oxadiazoles or furazans (p. 160). Reduction of α,γ-diisonitroso-β-oxoglutaric acid ester peroxide gives 4-**hydroxy-1,2,6-oxadiazine-3,5-dicarboxylic acid ester**:



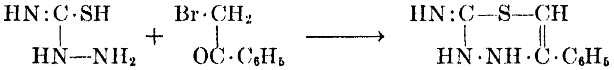
From this product a series of other oxadiazine derivatives have been obtained (*Henry, Pechmann*, Ber. **26**, 999).

3. Thiadiazines

(a) 4-**Phenyl-5,6-dihydro-1,4,3-thiadiazine-2(4)-thione**, m.p. 94°, is obtained by the condensation of phenylthiocarbazic acid with 1,2-dibromoethane (*Busch*, Ber. **27**, 2516):

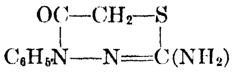


A similar reaction produces 2-imino-2,4-dihydro-1,4,3-thiadiazines from α-bromoacetophenone and thiosemicarbazide or a 4-alkyl derivative of it [*Bose, Ray-Chaudhury*, Quart. J. Indian Chem. Soc. **4** (1927), 257; *cf. Bose, ibid.* **3** (1926), 148]:



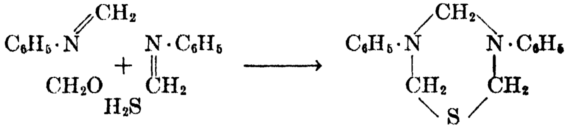
These thiadiazines are very weak bases. They form no acyl derivatives, and cannot be desulfurated.

2-Amino-4-phenyl-1,4,3-thiazin-5(6)-one:



m.p. 176°, is obtained by condensation of thiocyanoacetic acid with phenylhydrazine (*Harries, Klamt*, Ber. **33**, 1154).

(b) The products of the reaction of formaldehyde with primary aromatic amines in the presence of H_2S are derivatives of 1,3,5,2-**thiadiazine** [*Levi*, Atti acad.Lincei [6] **9** (1929), 790]:



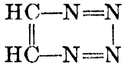
Thialdines (Vol. I, p. 247), produced by the action of ammonia on trithioaldehydes, are derivatives of 1,3,5-dithiazine.

IV. SIX-MEMBERED RINGS WITH FOUR HETERO ATOMS

TETRAZINES

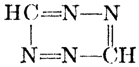
Of the three possible isomeric tetrazines:

(A)



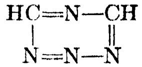
v-Tetrazine
1,2,3,4-Tetrazine

(B)



s-Tetrazine
1,2,4,5-Tetrazine

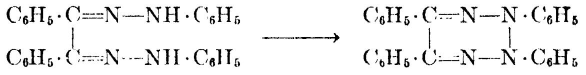
(C)



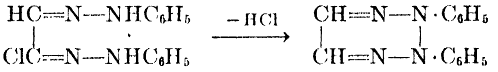
1,2,3,5-Tetrazine

derivatives of only the first two are known.

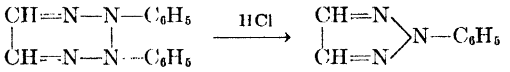
(A) **2,3-DIHYDRO-*v*-TETRAZINES, osotetrazines,** are prepared by oxidation of osazones:

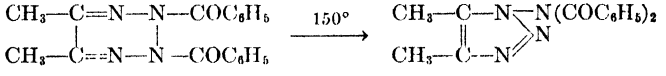


Chloroglyoxal osazone and its homologues are converted by treatment with alkali into diphenyl-2,3-dihydro-*v*-tetrazines, HCl being eliminated (*Dieckmann, Platz,* Ber. **38,** 2986):



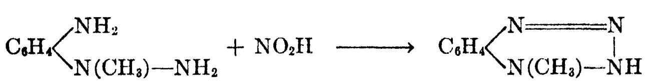
When heated alone or with mineral acids, the 2,3-dihydro-*v*-tetrazines rearrange to 2,1,3-triazoles (p. 147) (*Stollé,* Ber. **59,** 1742):



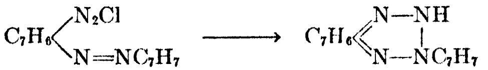


5,6-Diphenyl-2,3-dihydro-*v*-tetrazine, *glyoxalosotetrazine,* dark red flakes, m.p. 152°. **5,6-Dimethyl-2,3-diphenyl-2,3-dihydro-*v*-tetrazine,** m.p. 169°, bordeaux-red needles. **5,6-Dimethyl-2,3-dibenzoyl-2,3-dihydro-*v*-tetrazine,** colorless needles, m.p. 140°.

1-Methyl-1,2-dihydrobenzotetrazine, m.p. 62°, is obtained from *o*-aminophenylmethylhydrazine with nitrous acid (*Hempel,* J.pr. **41,** 176):

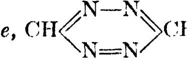


This compound corresponds to 1,2,3-benzotriazine, while the 2-aryl-2,3-dihydrobenzotetrazines are analogous to the 1,2,4-benzotriazines. They are prepared by reduction of the diazonium salts from *o*-aminoazo compounds (*Zincke, Lawsen,* Ber. **19,** 1457; *Zincke, Jaenke,* Ber. **21,** 543):



Azotoluene-2-diazonium chloride **2-Tolyl-7-methyl-2,3-dihydrobenzotetrazine, m.p. 168°.**

(B) **s-TETRAZINES** are formed by oxidation of their dihydro derivatives, and are characterized by their deep red color.

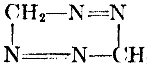
s-Tetrazine, 1,2,4,5-*tetrazine,* , purple-red prisms, m.p. 99°, sublimable, is prepd. by heating its dicarboxylic acid (see below). Hydrogen sulfide reduces it, with loss of color, to dihydrotetrazine, from which it is easily regenerated by oxidation (*Curtius, Darapsky, Müller,* Ber. **40,** 84).

3,6-**Dimethyl-s-tetrazine,** m.p. 74°, blue-red, from acetonitrile and anhydrous hydrazine, over its dihydro derivative (see below; *Curtius, Darapsky, Müller,* Ber. **48,** 1633). 3,6-**Diphenyl-s-tetrazine,** red flakes, m.p. 192°, by oxidation of 3,6-diphenyl-1,2-dihydro-s-tetrazine (p. 325) (*Pinner,* Ber. **27,** 984; *Pinner, Caro,* Ber. **27,** 3273; *Müller, Herrdegen,* J.pr. **102,** 113). **Di-*p*-tolyltetrazine,** m.p. 232° (*loc. cit.*); **di-2-naphthyltetrazine,** m.p. 249° (*loc. cit*).

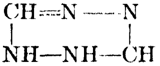
s-Tetrazine-3,6-dicarboxylic acid, carmine-red flakes, is prepared by the oxidation of *bis*-diazoacetic acid and *pseudo*-diazoacetic acid or their amides with nitrous acid or bromine. When warmed with water, it decomposes into N_2 and glyoxylhydrazino-oxalic acid, $CO_2H \cdot CH{:}N \cdot NH \cdot CO \cdot CO_2H$ (*Curtius, Darapsky, Müller,* Ber. **40,** 1176).

DIHYDRO-s-TETRAZINES. There are four possible isomers:

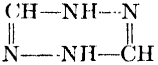
(I)



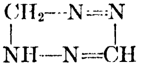
(II)



(III)

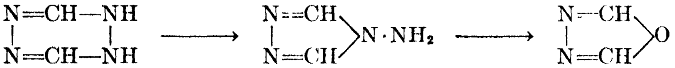


(IV)

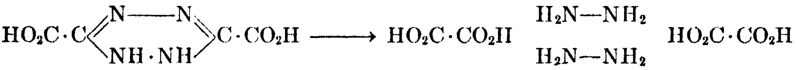


These were formerly called C-dihydrotetrazine, N,*v*-dihydrotetrazine, N,*s*-dihydrotetrazine and C,N-dihydrotetrazine; they are now known as 3,6-, 1,2-, 2,5-, and 1,6-dihydro-s-tetrazine.

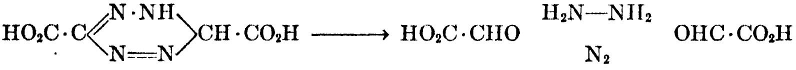
The 1,2-dihydrotetrazines are readily oxidized to the corresponding tetrazines, from which they can be obtained by reduction. When heated with concentrated acids, they are converted to 4-amino-4,1,2-triazoles (p. 156), which are then partially hydrolyzed to 1,3,4-oxadiazoles (see p. 163):



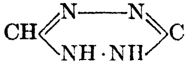
1,2-Dihydro-s-tetrazines are hydrolyzed by warm water or warm dilute acids; the two nitrogens linked by a single bond are converted to hydrazine, while the two joined by a double bond are split off as free nitrogen (Vol. I, p. 458; *Müller, Herrdegen,* J.pr. **102,** 123):



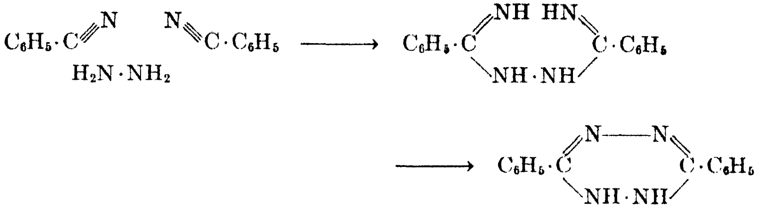
1,2-Dihydro-s-tetrazine-3,6-dicarboxylic acid = *Bis*-diazoacetic acid



1,6-Dihydro-s-tetrazine-3,6-dicarboxylic acid = Pseudo-diazoacetic acid

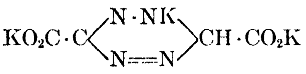
1,2-Dihydro-s-tetrazine, , bright yellow prisms, m.p. 126°, is obtained by reduction of s-tetrazine with hydrogen sulfide. When fused, it rearranges to 4-amino-4,1,2-triazole (see above). It is decomposed by mineral acids into hydrazine and formic acid (*Curtius, Darapsky, Müller,* Ber. **40,** 821).

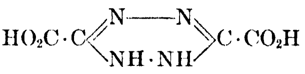
A general method for the preparation of dihydro-s-tetrazines is the reaction of hydrazines with nitriles:



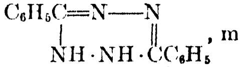
However, in many cases aminotriazoles are formed (*Hinsberg*, Ber. **48**, 1614; *Müller, Herrdegen*, J.pr. **102**, 113).

The polymerization products of diazoacetic ester are the intermediates for the formation of the simpler *s*-tetrazine and dihydro-*s*-tetrazine derivatives (*Curtius, Darapsky, Müller*, Ber. **41**, 3161; Vol. I, p. 458). When diazoacetic ester is treated with cold concentrated alkali, the product is the tripotassium salt of **1,6-dihydro-*s*-tetrazine-3,6-dicarboxylic acid**, *pseudo-diazoacetic acid* (I), from

(I) 

 (II)

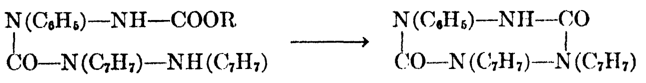
which the free acid has not yet been obtained. When heated with concentrated alkali the latter compound rearranges to **1,2-dihydrotetrazinedicarboxylic acid**; *bis-diazoacetic acid* (II), which is also formed directly by the action of warm concentrated alkali on diazoacetic ester. Prolonged heating with concentrated aqueous KOH solutions converts 1,6-dihydro-*s*-tetrazine-3,6-dicarboxylic acid to a mixture of N-*aminotriazoledicarboxylic acid* and C-*aminotriazolemonocarboxylic acid* (p. 157). 1,2-Dihydro-*s*-tetrazine-3,6-dicarboxylic acid decomposes on fusion into CO_2 and dihydrotetrazine; the latter rearranges immediately into N-aminotriazole.

1,2-Dihydro-3,6-diphenyl-*s*-tetrazine,  $\begin{matrix} C_6H_5C{=}N{-}N \\ | \qquad\quad \| \\ NH{\cdot}NH{\cdot}CC_6H_5 \end{matrix}$, m.p. 191°, yellow needles, is obtained by the action of excess hydrazine on benzimidic acid ester or benzonitrile (*Müller, Herrdegen*, J.pr. **102**, 113). It is converted to diphenyltetrazine (p. 324) by mild oxidizing agents, even by the oxygen of the air; the reverse reaction is effected by reduction with zinc dust and glacial acetic acid. When digested with hydrochloric acid, the diphenyldihydrotetrazine gives both *diphenyl*-1,3,4-*oxadiazole* (p. 164) and 4-*aminodiphenyl*-4,1,2-*triazole* (p. 156). For other 3,6-diaryl-1,2-dihydro-*s*-tetrazines, see *Müller, Herrdegen*, J.pr. **102**, 140 *ff*.

1,3,4,6-Tetraphenyl-1,4-dihydro-*s*-tetrazine, yellow needles, m.p. 204°, is prepared from phenylnitroformaldehyde hydrazone (the coupling product of phenylnitromethane with benzenediazonium chloride) with sodium methylate, or from benzaldehyde phenylhydrazone or dehydrobenzylidenephenylhydrazone with sodium alcoholate and iodine (*Bamberger, Grob*, Ber. **34**, 523).

1,2,4,5-Tetraphenylhexahydro-*s*-tetrazine, $(C_6H_5)_2N_2(CH_2)_2N_2(C_6H_5)_2$, m.p. 200°, from hydrazobenzene and formaldehyde (*Bischoff*, Ber. **31**, 3250; *Rassow, Rülke*, J.pr. **65**, 97).

A derivative of hexahydro-*s*-tetrazine is formed from phenyldibenzylcarbohydrazidecarboxylic acid ester with alcoholic KOH (*Busch*, Ber. **34**, 2311):



$$\begin{matrix} N(C_6H_5){-}NH{-}COOR \\ | \\ CO{-}N(C_7H_7){-}NH(C_7H_7) \end{matrix} \longrightarrow \begin{matrix} N(C_6H_5){-}NH{-}CO \\ | \qquad\qquad\quad | \\ CO{-}N(C_7H_7){-}N(C_7H_7) \end{matrix}$$

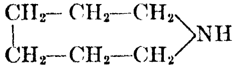
Pentazines, compounds containing five nitrogen atoms and one carbon atom in their ring, are not known (*cf. Stollé*, J.pr. 114, 348).

E. COMPOUNDS WITH HETEROCYCLIC RINGS OF MORE THAN SIX MEMBERS

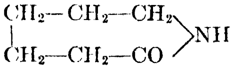
As in carbocyclic compounds, heterocyclic compounds with more than six members in their rings are relatively scarce (*cf.* p. 4). However, due to the multiplicity of reaction conditions which produce heterocyclic rings, it has been possible to prepare such rings with seven, eight, and more members. A systematic treatment of these substances, whose chemical behavior has not been fully investigated, is impractical. Therefore a summary of the compounds is given here. Note the occurrence of systems in which a benzene ring is condensed with a hetero-ring in the *meta*-position.

I. SEVEN-MEMBERED HETEROCYCLIC RINGS

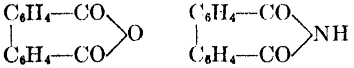
(The systematic names derived from the rules in "The Ring Index" are given in parentheses.)



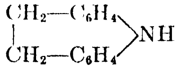
(Hexahydroazepine)
Hexamethylenimine (*v. Braun, Steindorff*, Ber. **38**, 3091)



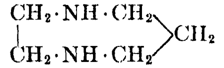
(Hexahydroazepinone-2)
ε-Caprolactam (Vol. I, p. 451)



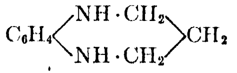
(5,7-Dihydrodibenz[*c*,*e*]oxepin- and azepine-5,7-dione)
Diphenic acid anhydride and imide (Vol. III, p. 506)



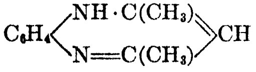
(10,11-Dihydro-5-dibenz[*b*,*f*]azepine)
Iminodibenzyl (*Thiele, Holzinger*, Ann. **305**, 100)



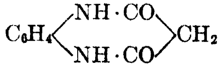
(Hexahydro-1,4-diazepine)
Ethylenetrimethylenediamine (*Howard, Marckwald*, Ber. **32**, 2041)



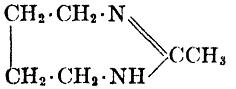
(2,3,4,5-Tetrahydro-1,5-benzodiazepine)
o-Phenylenetrimethylenediamine (*Hinsberg, Strupler*, Ann. **287**, 220)



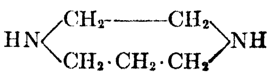
(2,4-Dimethyl-1,5-benzodiazepine)
(*Thiele, Steimmig*, Ber. **40**, 955)



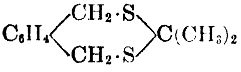
(1,5-Benzodiazepine-2,4(3,5)-dione)
o-Phenylenemalonimide (*Meyer, Maier*, Ann. **327**, 26)



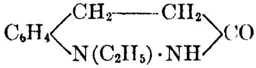
(2-Methyl-4,5,6,7-tetrahydro-1,3-diazepine)
Ethenyltetramethylenamidine (*Haga, Majima*, Ber. **36**, 338)



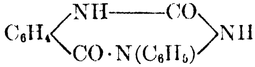
Homopiperazine
(Hexahydro-1,4-diazepine)
(*v. Braun, Goll*, Ber. **60**, 339)



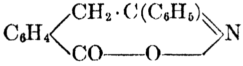
(3,3-Dimethyl-1,5-dihydro-2,4,3-benzodithiepin)
Acetone *o*-xylylenemercaptal
(*Autenrieth, Hennings*, Ber. **34**, 1775)



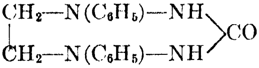
(1-Ethyl-4,5-dihydro-1,2-benzodiazepin-3(2)-one)
N-Ethylhydrocarbostyril (*Fischer*, Ann. **301**, 282)



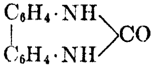
(4-Phenyl-1,3,4-benzotriazepine-2,5(3,4)-dione)
Carbonyl-*o*-aminobenzoylphenylhydrazine (*Rupe, Roesler*, Ann. **301**, 93)



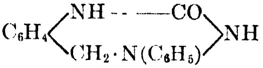
(4-Phenyl-2,3-benzoxazepin-1(5)-one)
Desoxybenzoin-*o*-carboxylic acid lactazone (*Gabriel*, Ber. **18**, 2449)



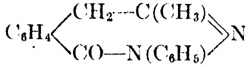
(1,5-Diphenyl-1,5,6,7-tetrahydro-2,1,4,5-tetrazepin-3(4)-one)
Carbonylethylenediphenylhydrazine (*Hischmann*, Ann. **310**, 156)



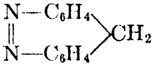
(Dibenzo[*d,f*][1,3]-diazepin-6(7)-one)
Carbonyl-*o,o'*-diaminodiphenyl
(*v. Niementowski*, Ber. **34**, 3330)



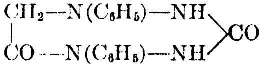
(4-Phenyl-4,5-dihydro-1,3,4-benzotriazepin-2(3)-one)
Carbonyl-*o*-aminobenzylphenylhydrazine (*Busch*, Ber. **27**, 2897)



(2-Phenyl-4-methyl-2,3,5-benzodiazepin-1(2)-one)
Methyl benzyl ketone-*o*-carboxylic acid phenyllactazam (*Gottlieb*, Ber. **32**, 966)

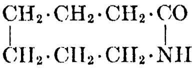


(11-Dibenzo[*c,f*][1,2]diazepine)
Azodiphenylmethane (*Freundler*, C.r. **136**, 1136)

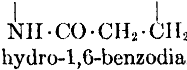


(1,5-Diphenyl-1,7-dihydro-2,1,4,5-tetrazepine-3,6(4,5)-dione)
Carbonylphenylhydrazidoacetphenylhydrazide (*Kneuppel*, Ann. **310**, 87).

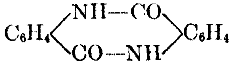
II. EIGHT-MEMBERED HETEROCYCLIC RINGS



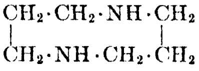
(Octahydro-2-azocinone)
Isosuberonoxime (Vol. I, p. 562)



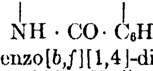
(3,4-Dihydro-1,6-benzodiazocine-2,5(1,6)-dione)
o-Phenylenesuccinamide (*Meyer, Maier*, Ann. **327**, 21)



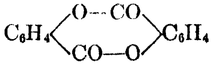
(Phenhomazine-6,12(5,11)-dione)
Dianthranilide



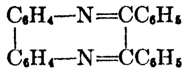
(Octahydro-1,5-diazocine)
Bistrimethylenediamine (*Howard, Marckwald*, Ber. **32**, 2038)



(Dibenzo[*b,f*][1,4]-diazocine-6,11(5,12)-dione)
o-Phenylenephthalamide (*Meyer, Maier*, Ann. **327**, 41)

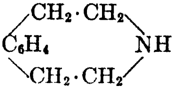


(Dibenzo[*b,f*][1,5]dioxocin-6,12-dione)
Disalicylide



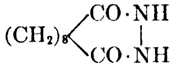
$$\begin{matrix} C_6H_4-N=CC_6H_5 \\ | \qquad\quad | \\ C_6H_4-N=CC_6H_5 \end{matrix}$$

(6,7-Diphenyldibenzo[*e,g*][1,4]-diazocine)
Diphenyldiphenoquinoxaline
Täuber, Ber. **26**, 1704)

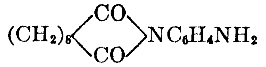


(*v. Braun*, *Karpf*, *v. Garn*, Ber. **53**, 98)

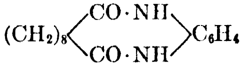
III. HETEROCYCLIC RINGS WITH MORE THAN EIGHT MEMBERS



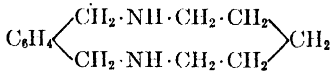
(1,2-Diazacyclododecane-3,12-dione)
sym-Sebacic acid hydrazide (Vol. I, p. 563)



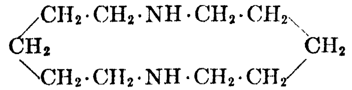
(1-*o*-Anilinoazacyclohendecane-2,11-dione)
Sebacic acid *o*-aminoanil (*Meyer*, Ann. **327**, 13)



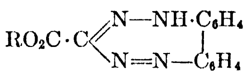
Sebacic acid *o*-phenylenediamide
(*Meyer*, Ann. **327**, 13)



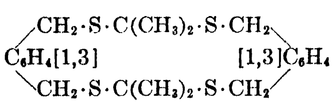
o-Xylylenepentamethylenediamine
(*Scholtz*, Ber. **31**, 1700)



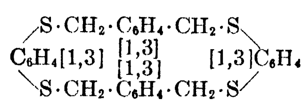
(1,7-Diazacyclododecane)
Bispiperidine
(*v. Braun*, *Blessing*, *Zobel*, Ber. **57**, 185)



Cycloformazylcarboxylic acid ester



(*Autenrieth*, *Beuttel*, Ber. **42**, 4357)



(*Reindel*, *Schuberth*, Ber. **57**, 370)

F. PLANT ALKALOIDS*

Certain compounds occuring in the juices of plants have long excited the curiosity of men, partly because of their curative action, but more especially because of their pronounced poisonous effect. Their isolation from the various parts of plants was therefore undertaken quite early in the development of organic chemistry. The first advance in this direction was the isolation of morphine (1806) from opium by the apothecary *Friedrich Wilhelm Sertürner*. Closer investigation disclosed that morphine was an alkaline substance, and that the basicity was due to the nitrogen content of the molecule, results that were startling at the time. These first important chemical facts to be known caused *W. Meissner* (1818) to name the basic compounds isolated from plants alkaloids, that is, substances resembling alkalis. The original concept of the term alkaloid was broadened by subsequent investigations to include other curative or very poisonous compounds containing nitrogen which had been isolated from plants, but which did not possess basic properties. The discovery of morphine prompted the investigation of other saps and led to the isolation of a large number of alkaloids. The following table gives the date of discovery of the most important of these:

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* *Winterstein-Trier*, Die Alkaloide (Borntraeger, Berlin, 1927). *T. A. Henry*, The Plant Alkaloids (Blakiston, Philadelphia, 1939). *R. Wolffenstein*, Die Pflanzenalkaloide (Springer, Berlin, 1922). *J. Schwyzer*, Die Fabrikation der Alkaloide (Springer, Berlin, 1927).

1806	Morphine (*Sertürner*)
1817	Narcotine (*Robiquet*)
1818	Strychnine (*Pelletier, Caventou*)
1819	Brucine (*Pelletier, Caventou*)
1819	Piperine (*Oerstedt*)
1820	Quinine (*Pelletier, Caventou*)
1820	Cinchonine (*Pelletier, Caventou*)
1826	Berberine (*Chevallier, Pelletan*)
1827	Coniine (*Giesecke*)
1828	Nicotine (*Posselt, Reimann*)
1831	Atropine (*Mein*)
1832	Codeine (*Robiquet*)
1833	Colchicine (*Geiger, Hesse*)
1848	Papaverine (*Merck*)
1860	Cocaine (*Niemann*)
1875	Pilocarpine (*Hardy*)
1921	Lobeline (*Wieland*)

From the foregoing list it is obvious that the original definition of "alkaloid" soon became too narrow; today it is impossible to formulate a simple definition broad enough to include all the compounds now classed as alkaloids.

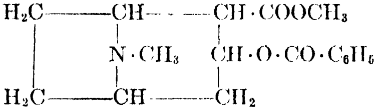
Many vegetable compounds containing nitrogen are treated in other parts of this series: caffeine, theobromine (Vol. I, pp. 643, 644), hordenine, ephedrine (Vol. III, pp. 337, 401), stachydrine, and many other pyrrolidine compounds (p. 49). This section will cover the important plant alkaloids of complicated structure based on the heterocyclic ring-systems described in this volume.

Many alkaloids have not only their nitrogen content in common, but also certain precipitation reactions. Many are precipitated by tannic acid, phosphotungstic acid, or phosphomolybdic acid, many form sparingly soluble double salts with platinum chloride or mercury potassium iodide. In a number of cases color reactions with chlorine water, concentrated nitric acid or concentrated sulfuric acid serve to identify alkaloids.

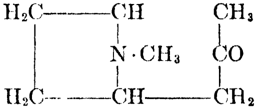
The alkaloids occur almost exclusively in plants of the dicotyledon family. A few, such as colchicine, have been isolated from monocotyledons. They often occur in plant saps combined with malic acid, citric acid, aconitic acid, tannic acid, or the like.

The alkaloids include derivatives of very varied types of compounds. Some are true bases (secondary and tertiary amines and ammonium compounds), while in others the nitrogen performs no basic function (acid amides). There are members of a great variety of ring-systems among them; the most common are pyridine, quinoline, and isoquinoline, but derivatives of imidazole and pyrrolidine also occur frequently. In some, the ring-system is a combination of two heterocyclic rings: piperidine and pyrrolidine in the tropane alkaloids, two piperidine rings in alkaloids of the pomegranate root bark, pyridine with indole in harmaline and harmine, isolated from *Peganum harmala* (p. 378).

Usually several chemically related alkaloids occur in the same plant sap. Cocaine is accompanied by hygrine, whose structure is similar:

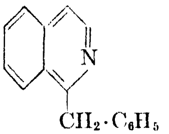


Cocaine



Hygrine

The alkaloids associated with morphine in opium, however, are derived from 1-benzylisoquinoline:



This structural relationship among the alkaloids of the same plant indicates that the plant synthesizes them from the same or very similar starting materials according to a single principle. As starting materials the plants can use cleavage products of proteins, carbohydrates, and their decomposition products (C_6- and C_3-chains), and perhaps also formaldehyde. For investigations of the reaction mechanism of the synthesis of alkaloids by plants, see *Pictet*, *Spengler*, Ber. **44,** 2032; *Emde,* N. **1929,** 699.

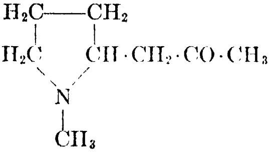
A number of alkaloids have been synthesized in the laboratory. *Ladenburg* (1886) prepared the relatively simple coniine and separated it into its optically active components with tartaric acid. This first synthesis was followed by others of more complicated alkaloids: nicotine (*Pictet*), tropane alkaloids (*Willstätter*), and many members of the isoquinoline series (*Späth* and others).

It is very difficult to make an adequate systematic division of the alkaloids. A truly adequate system will be possible only when the biogenic synthesis of alkaloids is understood sufficiently to permit the separation of these compounds into families according to their natural genetic relationship. The beginnings of such a system have already been made (see above). The classification used here is necessarily based on purely external evidence of the constitution of the alkaloids, such as the ring-systems occurring in their decomposition products, and therefore is far from ideal.

I. ALKALOIDS OF THE PYRROLIDINE GROUP

This group includes several alkaloids which have been found together with cocaine:

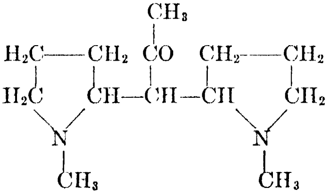
Hygrine, $C_8H_{15}N$, b.p. 92–94° (20 mm.), $[\alpha]_D$ −1.3°; picrate, m.p. 158°. Hygrine forms a crystalline oxime (m.p. 116°) (*Liebermann, Kühling,* Ber. **26,** 851) and is oxidized by chromic acid to hygrinic acid, 1-methylpyrrolidine-2-carboxylic acid (p. 49; *Liebermann, Cybulski,* Ber. **28,** 582; *Willstätter, Ettlinger,* Ann. **326,** 123), which gives 1-methylpyrrolidine when decarboxylated. These facts, together with the ketone properties and empiric formula of hygrine, point to this structure:



(Hygrine = 1-Methyl-2-acetonylpyrrolidine)

This formula has been verified by the synthesis of *dl*-hygrine (*Hess,* Ber. **46,** 3113, 4104).

Cuskhygrine, $C_{13}H_{24}ON_2$, b.p. 185° (32 mm.), optically inactive, occurs in cuzco leaves. This alkaloid is also a ketone (oxime, m.p. 54°), and both of its nitrogen atoms are tertiary. It oxidizes to hygrinic acid. Its structure is given by the following formula (*Hess, Fink,* Ber. **53,** 781; *Hess, Anselm,* Ber. **54,** 2310):



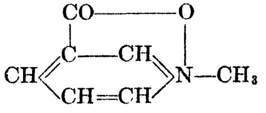
(Cuskhygrine = α,α-Di-(1-methyl-2-pyrrolidinyl)-acetone)

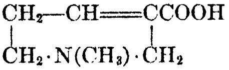
Stachydrine, see p. 49.
Nicotine, see p. 336.

II. ALKALOIDS OF THE PYRIDINE GROUP

TRIGONELLINE, *nicotinic acid methylbetaine,* (I), m.p. 218°, anhydrous, occurs in the fenugreek seeds of *Trigonella foenum graecum* and in very small amounts, together with choline, in the seeds of peas, *Pisum sativum,* of hemp, *Cannabis sativa,* and of *Strophanthus* types (*Thoms,* Ber. **31,** 271); it has also been detected in several kinds of coffee (*Garter,* Ann. **372,** 239). *Jahns* has proved that trigonelline is identical with the nicotinic acid betaine synthesized by *Hantzsch* in 1886 (*Schulze, Frankfurt,* Ber. **27,** 769).

ARECAIDINE (*arecaine*), $C_7H_{11}NO_2$, 1-methyltetrahydronicotinic acid (II),

(I) 

 (II)

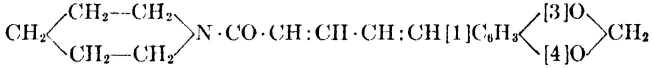
$$\begin{array}{l} CH_2\text{—}CH{=\!=}CCOOH \\ CH_2\cdot N(CH_3)\cdot CH_2 \end{array}$$

m. p. 232° (*Hess, Leibbrandt,* Ber. **52,** 206), is found together with **arecoline,** $C_8H_{13}NO_2$, b.p. 220° (principal constituent), and **guvacine,** $C_6H_9NO_2$, m.p.

293° (*Winterstein, Weinhagen,* Z.physiol.Chem. **104,** 48), in the betel nut of *Areca catechu,* where **arecolidine,** $C_8H_{13}O_2N$, m.p. 110° [*Emde,* Apoth.Ztg. **30** (1915), 240], and **guvacoline,** b.p. 114° (23 mm.) (*Hess,* Ber. **51,** 1004), have also been detected. Arecaidine has been synthesized from 1-methyl-1,2,5,6-tetrahydro-3-pyridinecarboxaldoxime (p. 220) by conversion to the nitrile and then saponification (*Wohl, Johnson,* Ber. **40,** 4712). It is also formed, together with its dihydro derivative, **dihydroarecaidine,** 1-*methylhexahydronicotinic acid,* from the methyl chloride addition product of nicotinic acid ester by reduction with tin and hydrochloric acid. When saponified with methanol and HCl, it yields **arecoline,** b.p. 209°, which regenerates arecaidine on saponification and is, therefore, 1-*methyl-tetrahydronicotinic acid methyl ester* (*Jahns,* Arch.Pharm. **229** (1882), 669; *Willstätter,* Ber. **30,** 729; *Meyer,* Mo. **23,** 22).

Guvacine, $C_6H_9NO_2$, and **guvacoline,** $C_7H_{11}NO_2$, are the corresponding (methyl-free) tetrahydronicotinic acid (*Freudenberg,* Ber. **51,** 976; *Hess,* Ber. **51,** 1004) and its methyl ester (*Hess,* Ber. **51,** 1004). Methylation converts them to the methyl iodide addition product of arecoline. The constitution of arecolidine is not entirely clear.

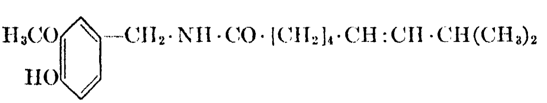
PIPERINE, $C_{17}H_{19}NO_3$, (III), m.p. 128°, optically inactive, occurs in different varieties of pepper, the fruit of *Piper nigrum* and *Piper longum.* When digested with alcoholic KOH, it decomposes into piperidine (p. 220) and piperic acid; it dissolves in concentrated sulfuric acid to a dark red solution.

(III) 

$$CH_2\left\langle\begin{matrix}CH_2\text{—}CH_2\\CH_2\text{—}CH_2\end{matrix}\right\rangle N\cdot CO\cdot CH:CH\cdot CH:CH[1]C_6H_3\left\langle\begin{matrix}[3]O\\ [4]O\end{matrix}\right\rangle CH_2$$

Since the two decomposition products of piperine have been prepared from their elements, and piperine has been synthesized from them by the reaction of piperic acid chloride with piperidine, the constitution of piperine is known without doubt (*Ladenburg, Scholtz,* Ber. **27,** 2958). Artificial piperines have been obtained from the chlorides of synthetic 2-alkyl- and 2-phenylpiperic acids (*Scholtz,* Ber. **28,** 1195). *Tetrahydropiperine,* $C_{17}H_{23}NO_3$, b.p. 280° (16 mm.) (*Borsche,* Ber. **44,** 2942).

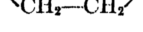
In connection with the constitution of piperine, experiments have been performed to determine the relation between constitution and pepper taste (*Staudinger,* Ber. **56,** 699). It was found that the sharp pepper taste is a property of the acid amide structure, especially when the nitrogen is a member of a piperidine ring. As acid components aliphatic-aromatic carboxylic acids increase the pepper taste. However, **capsaicine** (IV), $C_{18}H_{27}O_3N$, m.p. 65°, the sharp constituent of the *Capsicum* fruit (paprika), is an acid amide, but does not contain a piperidine ring



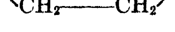
(IV)

(*Nelson,* Am. **41,** 1115, 1472, 2121; **42,** 597; *Nelson, Dawson,* Am. **45,** 2179). Capsaicine decomposes on hydrolysis to 4-hydroxy-3-methoxybenzylamine and an isodecylenic acid. The complete synthesis of capsaicine has been accomplished by *Späth* (Ber. **63,** 737).

CONIINE (V), 2-*n-propylpiperidine,* $C_8H_{17}N$, b.p. 165.8°, d^{20} 0.844, $[\alpha]_D^{19} = +15.7°$, is found together with N-methylconiine, b.p. 176°, γ-coniceine (VI), b.p. 172° (*v. Braun, Steindorff,* Ber. **38,** 3094; synthesis: *Gabriel,* Ber. **42,** 4059), conhydrine and pseudoconhydrine (p. 334) in hemlock, *Conium maculatum,* especially in the seeds. For the separation of these alkaloids, see *v. Braun,* Ber. **38,** 3108. Coniine is a colorless liquid with a stupefying odor; it is a very powerful poison.

(V) 

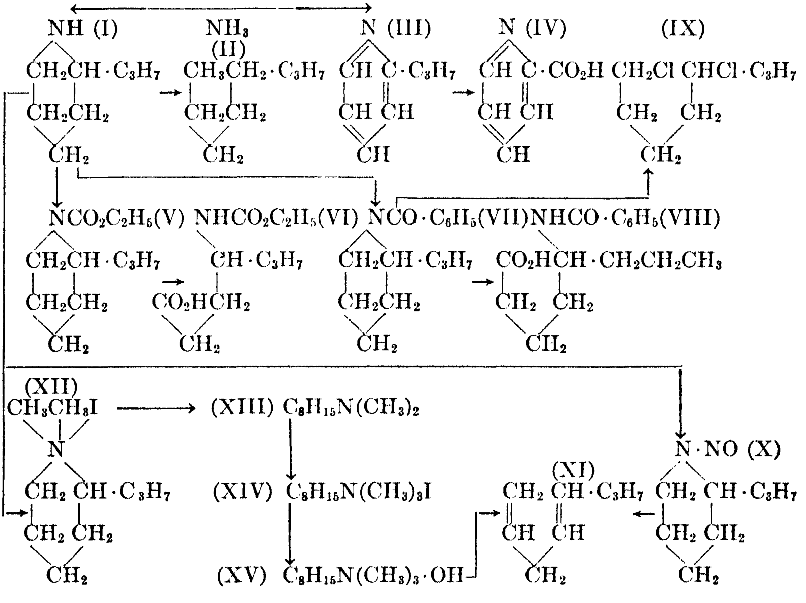
$$CH_2\left\langle\begin{matrix}CH_2\text{—}CH\text{—}CH_2CH_2CH_3\\CH_2\text{—}CH_2\end{matrix}\right\rangle NH$$

 (VI)

$$CH_2\left\langle\begin{matrix}CH\text{=}C(C_3H_7)\\CH_2\text{——}CH_2\end{matrix}\right\rangle NH$$

History.—Coniine was discovered by *Giesecke* in 1827. In 1881 *A. W. Hofmann* determined its molecular weight, and in 1884 he demonstrated that it is converted to conyrine or 2-propylpyridine by distillation over zinc dust. *Hofmann* proved the 2-position of the propyl group by oxidation of the propylpyridine to picolinic acid. The synthesis of optically inactive coniine and its resolution into *d*- and *l*-coniine, which comprised the first complete synthesis of an optically active plant alkaloid, were accomplished by *Ladenburg* in 1886 (Ber. **22**, 1403).

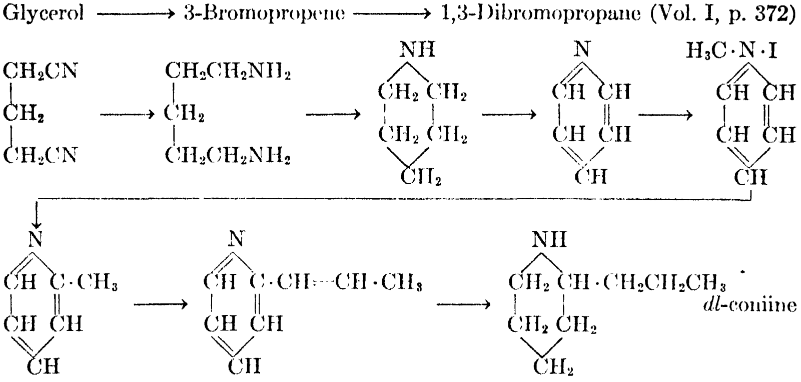
Decomposition of Coniine.—Reduction of natural *d*-coniine (I) with HI yields *n*-octane (II) and NH_3 (*Hofmann*, Ber. **18**, 13). The distillation with zinc dust gives conyrine (III), 2-*n*-propylpyridine, which is converted by reduction with sodium and alcohol to the inactive *dl*-coniine, and by oxidation to picolinic acid, pyridine-2-carboxylic acid (IV). The N-carbethoxy derivative of coniine (V) is oxidized by nitric acid to carbethoxyconiinic acid, γ-carbethoxyaminoenanthic acid (VI) (*Schotten*, Ber. **15**, 1947), which yields coniinic acid when heated with hydrochloric acid. 1-Benzoylconiine (VII) is oxidized by $KMnO_4$ to benzoylhomoconiinic acid, γ-benzoylaminocaprylic acid (VIII), and α-benzoylaminovaleric acid. With PCl_5 benzoylconiine gives 1,5-dichlorooöctane (IX) (*v. Braun, Schmitz*, Ber. **39**, 4365). Nitrous acid converts coniine to nitrosoconiine (X), which decomposes when heated with phosphorus pentoxide into water, nitrogen, and conylene (XI). Coniine adds methyl iodide to form 1,1-dimethylconiinium iodide (XII), which is transformed by aqueous sodium hydroxide to the so-called dimethylconiine, $C_8H_{16}N(CH_3)_2$ (XIII). The latter is not a single compound, but a mixture of a little methylconiine and two isomeric bases formed by splitting the piperidine ring between the N and 2-C atom and between the N and 6-C atom, respectively. With methyl iodide these isomeric bases give iodides, (XIV), which are hydrolyzed by silver oxide to the so-called trimethylconiinium hydroxide (XV); the latter decomposes on distillation into water, trimethylamine and conylene (XI). Dimethylconiine reacts energetically with hydriodic acid; reduction of the hydriodide so formed gives a mixture of two saturated bases, one of which has been identified by means of its methyl iodide addition product with dimethyl-*n*-octylamine (*Mugdan*, Ann. **298**, 131):



Synthesis of Coniine **(*Ladenburg*, Ber. 22, 1404; 40, 3734; *Hess, Weltzien*, Ber. 53, 145).**—The synthesis of coniine starts with the preparation of glycerol, either from acetic acid or from nitromethane (Vol. I, p. 580). Glycerol is converted to 3-bromopropene, which is treated with hydrobromic acid to form 1,3-dibromopropane. The latter gives glutaronitrile, which is reduced to pentamethylenediamine; from this, piperidine is formed by elimination of ammonia. Piperidine can be oxidized to pyridine, whose methyl iodide addition product rearranges to 2-picolinium iodide when heated at 300°. 2-Picoline condenses with paraldehyde to give α-methyl-2-pyridineëthanol, which can be reduced by successive treatment with hydriodic acid and zinc dust to 2-*n*-propylpyridine, or can be converted to 2-propenylpyridine by heating with concentrated hydrochloric acid. The latter compound is also obtained directly by heating 2-picoline with paraldehyde at a high temperature. Reduction of either 2-propyl- or 2-propenylpyridine with sodium and alcohol gives inactive coniine.

For another synthesis of *dl*-coniine, starting from 2-pyridinecarboxaldehyde with ethylmagnesium bromide, see *Lautenschläger, Onsager*, Ber. **51**, 602; from 2-picoline with chloral, see *Koller*, Mo. **47**, 393.

d-Coniine *d*-tartrate separates first from a solution of *dl*-coniine *d*-tartrate; it is hydrolyzed by alkali to the *d*-coniine, $[\alpha]_D = +17.85°$ (*Hess, Weltzien*, Ber. **53**, 145).

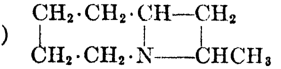


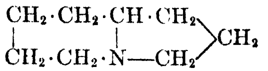
***d*-Coniine hydrochloride**, m.p. 218°; platinum salt, m.p. 175°; gold salt, m.p. 77°. **Nitrosoconiine**, bright yellow oil. ***d*-N-Carbethoxyconiine**, b.p 245°. ***d*-Benzoylconiine**, viscous oil, b.p. 204° (16 mm.).

Synthesis of *l*-coniine: *Löffler, Friedrich*, Ber. **42**, 115.

The inactive *dl*-coniine and the *l*-coniine have the same chemical and physiological properties as *d*-coniine. Inactive coniine is best prepared by reduction of γ-coniceine (p. **332**) (*Wolffenstein*, Ber. **29**, 1956).

Two isomeric alkaloids containing oxygen, ***conhydrine***, m.p. 120°, b.p. 226°, $[\alpha]_D$ +10°, and ***pseudoconhydrine***, m.p. 106°, b.p. 236°, $[\alpha]_D$ +11°, are found with coniine in hemlock. The former has been found to be one of the optically active forms of α-ethyl-2-piperidinemethanol, $(C_5H_9NH)CH(OH)CH_2CH_3$ (p. 224; *Löffler, Tschunke*, Ber. **42**, 929; *Hess, Eichel*, Ber. **50**, 1386). The pseudoconhydrine is probably a derivative of coniine hydroxylated in the piperidine nucleus. By successive treatment with hydriodic acid and zinc dust conhydrine is converted to *l*-coniine, and pseudoconhydrine to *d*-coniine. When conhydrine is treated with dehydrating agents such as P_2O_5 or concentrated hydrochloric acid, γ-coniceine (p. **332**), which occurs in nature, is formed in small amounts, and a larger quantity of the isomeric β-coniceine, 2-propenylpiperidine, $(C_5H_9NH)CH{:}CH{\cdot}CH_3$, is produced in two stereoisomeric forms (see p. 224). The iodides obtained from these by addition of hydriodic acid undergo intramolecular alkylation when treated with alkali, yielding the tertiary, saturated bicyclic ε-coniceine (I). An isomer of this base, δ-coniceine (II), has been prepared from coniine by bromination with hypobromite and subsequent elimination of HBr by means of concentrated H_2SO_4; see the corresponding inactive form of this base (p. 224) (*Löffler, Kaim*, Ber. **42**, 94; *Löffler, Tschunke*, Ber. **42**, 929).

(I) 

 (II)

Associated with the principal alkaloid, *pseudopelletierine* (p. **348**), of the pomegranate root bark (*Punica granatum*) are several others which are related to coniine:

Pelletierine, $C_8H_{15}ON$, b.p. 106° (21 mm.), inactive, resolvable into antipodes through the bitartrate (*Hess, Eichel,* Ber. **51**, 741); hydrobromide, m.p. 140°.

Isopelletierine, $C_8H_{15}ON$, b.p. 102–107° (11 mm.); hydrobromide, m.p. 149°.

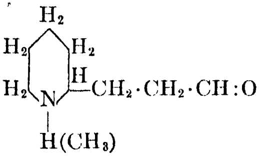
Methylpelletierine, $C_9H_{17}ON$, b.p. 106–108° (45 mm.), $[\alpha]_D$ +27.7° (without solvent); hydrobromide, m.p. 165°, $[\alpha]_D$ +33.5°.

Methylisopelletierine, $C_9H_{17}ON$, b.p. 95° (12 mm.); hydrochloride, m.p. 158°; picrate, m.p. 154°. Resolvable into optical antipodes (*Hess, Eichel,* Ber. **51**, 741).

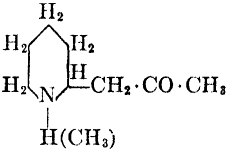
Methylisopelletierine is converted to isopelletierine by oxidation with chromic acid in boiling glacial acetic acid (*Meisenheimer, Mahler,* Ann. **462**, 305), while the reverse reaction, the methylation, takes place less readily. Its constitution is determined by correlation of the following data:

The oxygen of *pelletierine* is present in an aldehyde group, since it forms an oxime, which can be converted with PCl_5 to a nitrile which saponifies to *2-piperidinepropionic* acid. The hydrazone of pelletierine reduces to *dl*-coniine.

Methylisopelletierine also contains a carbonyl group (semicarbazone, m.p. 169°), which is a ketone group according to the results of the oxidation with chromic acid in sulfuric acid solution. This oxidation yields acetic acid and *1-methylpiperidine-2-carboxylic acid* (*1-methylpipecolinic acid*) (*Hess,* Ber. **52**, 970). Since the hydrazone of methylisopelletierine is converted by reduction with sodium and alcohol to *dl*-N-*methylconiine*, it is probable that methylisopelletierine is 1-methyl-2-acetonylpiperidine. This supposition has been verified by the conversion of the synthetic 1-(*1-methyl-2-piperidine*)*-2-propanol* by chromic acid in glacial acetic acid to *methylisopelletierine* (*Meisenheimer, Mahler,* Ann. **462**, 310):



Pelletierine,
Methylpelletierine



Isopelletierine,
Methylisopelletierine

The constitution of the alkaloids of the lobelia plants (*Lobelia inflata*), which contain a piperidine ring, has also been completely proved.

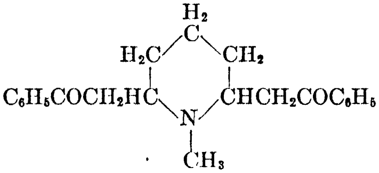
Principal alkaloid: **lobeline,** $C_{22}H_{27}O_2N$, m.p. 130°, $[\alpha]_D$ −42.8° (alcohol) (*Wieland,* Ber. **54**, 1784). Other alkaloids: **lobelanine,** $C_{22}H_{25}O_2N$, m.p. 99°, optically inactive, hydrochloride m.p. 188° (*Wieland, Schöpf, Hermsen,* Ann. **444**, 49); **lobelanidine.** $C_{22}H_{29}O_2N$, m.p. 150°, optically inactive, hydrochloride m.p. 138° (*loc. cit.*, p. 56); *dl*-**lobeline** (= lobelidine), $C_{22}H_{27}O_2N$, m.p. 110°; **norlobelanine,** $C_{21}H_{23}O_2N$, m.p. 121° (*Wieland, Koschera, Dane,* Ann. **473**, 122); **norlobelanidine,** $C_{21}H_{27}O_2N$, m.p. 120° (*loc. cit.*, p. 124).

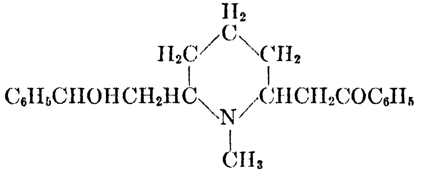
The first three alkaloids mentioned above are interconvertible by simple chemical reactions. Nascent hydrogen reduces lobelanine (a diketone) to lobeline (a hydroxy ketone) and then to lobelanidine (dihydric alcohol), which yields some lobelanine when oxidized with chromic acid in glacial acetic acid. The nitrogen atom is a member of the ring and carries a methyl group. Norlobelanine and norlobelanidine are the corresponding methyl-free secondary bases; they can be methylated with methyl *p*-toluenesulfonate to lobelanine and lobelanidine (*Wieland, Koschera, Dane,* Ann. **473**, 124).

More information concerning their constitution is given by the Hofmann decomposition of lobelanine. Its methyl iodide addition product loses trimethylamine very readily when treated with silver oxide, forming a doubly unsaturated compound, which is converted by catalytic hydrogenation to a diketone, 1,7-

dibenzoyl-n-heptane. Alkali fusion splits lobelanine into *acetophenone, benzohydrol,* and *methylamine.* The dioxime of lobelanine (m.p. 209°, dec.) undergoes a *Beckmann* rearrangement when treated with $SOCl_2$, yielding a dianilide, which can be saponified to *lobelinic acid,* 1-*methylpiperidine*-2,6-*dicarboxylic acid,* m.p. 228° (dec.). Lobelanine is oxidized by chromosulfuric acid to *scopolinic acid,* 1-*methylpiperidine*-2,6-*dicarboxylic acid,* m.p. 225°.

From these data it follows that **lobelanine** is 1-*methyl*-2,6-*phenacylpiperidine* (I), and the structure of **lobeline** (II) and **lobelanidine** may be deduced from the simple relationships mentioned above (*Wieland, Dragendorff,* Ann. **473,** 83):

(I) 

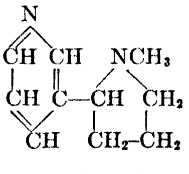
 (II)

Lobelanidine is the corresponding dihydric alcohol.

This interpretation of the structure of the lobelia alkaloids is supported by two independent syntheses of norlobelanidine (*Wieland, Drishaus,* Ann. **472,** 102, 106).

Lobeline is a specific agent for the stimulation of the respiratory center, and is therefore one of the best remedies for asthma.

NICOTINE (III), 1-*methyl*-2-(3-*pyridyl*)-*pyrrolidine,* $C_{10}H_{14}N_2$, b.p. 247°, d_4^{20} 1.00924, $[\alpha]_D^{20}$ −169.22° (*Ratz,* Mo. **26,** 1241), occurs in the leaves of the tobacco plants, *Nicotiana tabacum,* in amounts up to 0.6–8%.

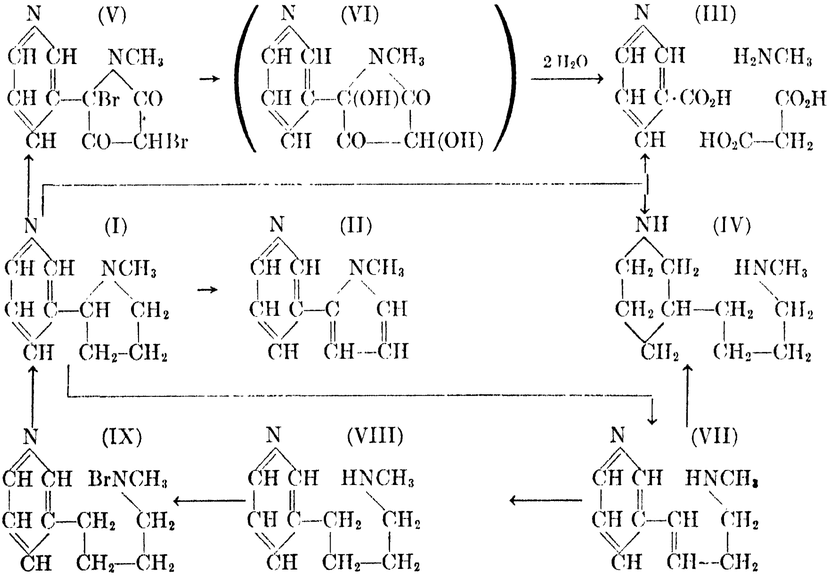
(III) 

Some subsidiary alkaloids are found in the tobacco lye: **nicoteine,** $C_{10}H_{12}N_2$, b.p. 267°, $[\alpha]_D$ −46.41°, ditertiary base, gives nicotinic acid when oxidized; **nicotelline,** $C_{10}H_8N_2$, m.p. 148°, and **nicotimine,** $C_{10}H_{14}N_2$, b.p. 150–155°, a tertiary-secondary base isomeric with nicotine, and small quantities of pyrrolidine and 1-methylpyrroline [*Pictet, Rotschy,* Ber. **34,** 696; *Pictet, Court,* Ber. **40,** 3773; *Pictet,* Arch.Pharm. **244** (1906), 375].

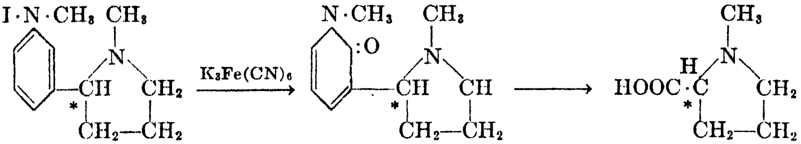
Nicotine is readily soluble in water. It has a disagreeable odor and a burning taste. It is a violent poison. The salts of nicotine are dextrorotatory: hydrochloride, $[\alpha]_D$ +102°; sulfate, $[\alpha]_D$ +85°; acetate, $[\alpha]_D$ +110.2°.

History.—Nicotine was discovered in 1828 by *Posselt* and *Reimann.* Its reaction products have been studied since 1891 by *Blau* and by *Pinner.* The structure proposed by the latter is in agreement with the chemical behavior of nicotine and has more recently been verified by the investigations of *Amé Pictet* and his students (1895–1904) and of *Späth* (*Späth, Bretschneider*, Ber. **61**, 327), which have led to the synthesis of nicotine.

Nicotine (I) (see the diagram below) is a ditertiary base. It forms an addition product with two molecules of methyl iodide, and two isomeric products with one molecule, one of which yields trigonelline (p. 331) on oxidation. Oxidation with potassium ferricyanide, or better with silver oxide, or dehydrogenation with Pd (*Wibaut, Overhoff*, Rec. **47**, 935), converts nicotine to nicotyrine (II), 1-methyl-2-(3-pyridyl)pyrrole (*Blau*, Ber. **27**, 2535). Nitric acid, chromic acid or potassium permanganate oxidizes nicotine to nicotinic acid (III), 3-pyridinecarboxylic acid (*Laiblin*, Ann. **196**, 130; *cf. Pictet, Genequand*, Ber. **30**, 2122). Sodium and alcohol reduce it to hexahydronicotine and, with rupture of the pyrrolidine ring, to octahydrometanicotine (IV) (*Pinner*, Ber. **26**, 765). With bromine and water nicotine forms dibromoticonine (V), $C_{10}H_8Br_2N_2O_2$, which decomposes in barium hydroxide solution through (VI) to methylamine, malonic acid, and nicotinic acid (III) (*Pinner*, Ber. **26**, 292). With benzoyl chloride nicotine forms an addition product, from which nicotine can be regenerated with hydrochloric acid; when treated with sodium alcoholate this product yields a secondary base isomeric with nicotine, metanicotine (VII), 3-(4-methylamino-1-butenyl)-pyridine, b.p. 275–278°. The latter is reduced by sodium and alcohol to hexahydrometanicotine, and octahydrometanicotine (IV), which is also obtained directly from nicotine, and by HI and red phosphorus to dihydrometanicotine (VIII). With sodium hypobromite the dihydrometanicotine forms an N-bromo derivative (IX), which is converted by elimination of HBr with warm concentrated sulfuric acid to nicotine (I):



The stable pyridine ring can be recovered from the nicotine molecule as nicotinic acid or trigonelline by oxidation according to the methods mentioned above. The more difficult problem of isolating the intact pyrrolidine ring has also been solved. *l*-Hygrinic acid, *1-methylpyrrolidine-2-carboxylic acid*, is obtained from the *Py*-methyl iodide of nicotine, which is oxidized by potassium ferricyanide to N-*methylnicotone*, from which *l*-hygrinic acid can be isolated in 25% yield by oxidation with CrO_3 (*Karrer, Widmer*, Helv. **8**, 364):



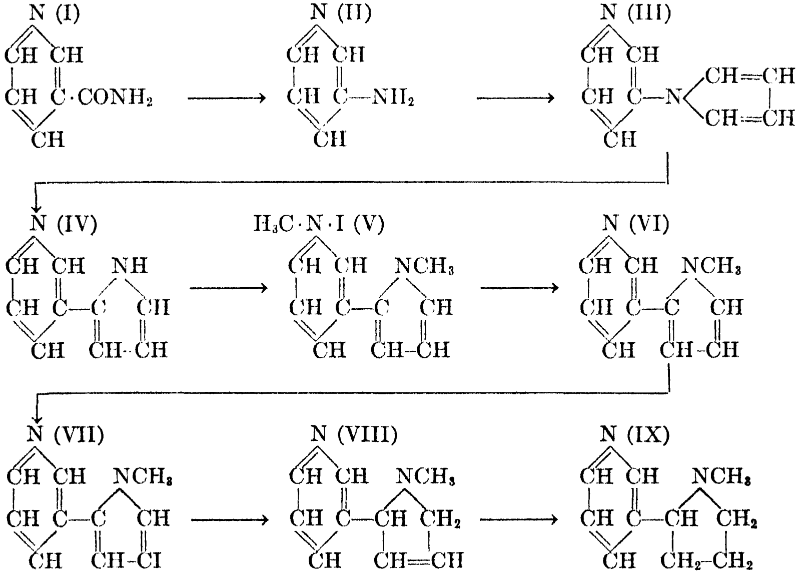
Py-Nicotine methyl iodide

N-Methylnicotone

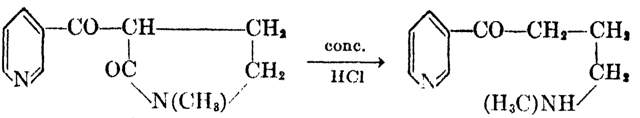
l-Hygrinic acid

This sequence of reactions also gives information concerning the configuration of the asymmetric carbon atom (*) in nicotine.

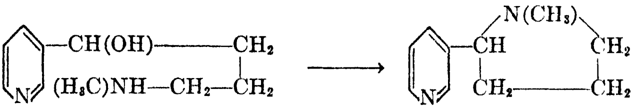
Synthesis of nicotine according to Pictet (see the scheme below).—Nicotinamide (I) is converted by potassium hypobromite to 3-aminopyridine (II), which yields 1-(3-pyridyl)-pyrrole (III) when distilled with mucic acid. Passage through a slightly incandescent tube rearranges 1-(3-pyridyl)-pyrrole to 2-(3-pyridyl)-pyrrole (IV), which adds methyl iodide to give N-methylnicotyrinium iodide (V) (*Söderbaum*, Ber. **28**, 1909). Distillation with CaO splits off methyl iodide, leaving *nicotyrine* (VI), which can be converted to nicotine by this series of reactions: Nicotyrine reacts with iodine to give *iodonicotyrine* (VII), which is reduced by zinc dust and aqueous sodium hydroxide to *dihydronicotyrine* (VIII). The latter is further reduced by treatment of its bromination product with tin and hydrochloric acid to *tetrahydronicotyrine* (IX), which is identical with the inactive nicotine prepared by heating solutions of nicotine salts at 180–250°. The inactive nicotine (tetrahydronicotyrine) can be resolved by means of its bitartrate into *l-nicotine*, identical with the natural nicotine, and *d-nicotine*, $[\alpha]_D$ +163.17°, which is far less poisonous than the natural nicotine (*Pictet, Rotschy*, Ber. **37**, 1225; *Pictet*, C. r. **137**, 862).



Another synthesis, with somewhat milder reagents, has been developed by *Späth* (*Späth, Bretschneider*, Ber. **61**, 327). Ethyl nicotinate is condensed by an acetoacetic acid condensation with 1-methylpyrrolidine to 3-pyridyl 1-methyl-2-oxo-3-pyrrolidyl ketone (X). Concentrated hydrochloric acid splits the pyrrolidine ring and removes CO_2, leaving the base (XI), which is converted through its carbinol (XII) to *dl*-nicotine (XIII).



(X) (XI)

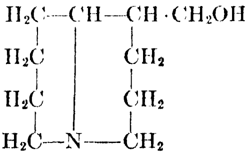


(XII) (XIII)

SPARTEINE (*lupinidrine*), $C_{15}H_{26}N_2$, b.p. 325°, d^{20} 1.02, $[\alpha]_D$ −16.42°, is a colorless, viscous oil, which occurs in the broom, *Sarothamnus scoparius*, with the subsidiary alkaloids, **sarothamnine**, $C_{15}H_{24}N_2$, and **genisteine**, $C_{16}H_{28}N_2$, m.p. 60.5°, b.p. 140° (5 mm.) (*Valeur*, C.r. **167**, 26, 163). Sparteine is a saturated, diacid, ditertiary base, which contains no free methyl groups attached to the nitrogen. Since the presence of an aromatic nucleus is improbable, the ring system of sparteine must be assumed to contain four saturated rings. With chromic acid or alkaline potassium ferricyanide solution, it is oxidized to *hydroxysparteine*, $C_{15}H_{24}ON_2$, and with hydrogen peroxide, to *sparteine oxide*, $C_{15}H_{24}O_2N_2$, from which sparteine can be readily obtained; with chromic acid an unsaturated base, *spartyrine*, $C_{15}H_{24}N_2$, and a neutral compound, $C_{15}H_{24}O_4N_2$, are also formed (*Wackernagel*, *Wolffenstein*, Ber. **37**, 3238; *Willstätter*, *Marx*, Ber. **38**, 1772; *Ahrens*, Ber. **38**, 3268). *Dehydrosparteine*, $C_{15}H_{24}N_2$, gold salt m.p. 158°, from sparteine with mercuric acetate [*Winterfeld*, Ber.deut.pharm.Ges. **266** (1928), 299], is oxidized by $KMnO_4$ to an acid, $C_{14}H_{24}O_2N_2$, Pt salt of the methyl ester m.p. 257° (dec.), which yields an amine, $C_{13}H_{25}N_3$, picrate m.p. 187° (dec.), and *2-methylpyrrolidine*, gold salt m.p. 184° [*Winterfeld*, Arch. Pharm. **267**, (1929), 433]. The same compound is oxidized by chromic acid in sulfuric acid solution to the N-methyl derivative of a *2-methylpyrrolidinecarboxylic acid*, $C_7H_{13}O_2N$, Pt salt m.p. 250° [*Winterfeld*, *Ipsen*, Arch.Pharm. **268**, (1930) 372]. The methylsparteinium hydroxide, obtained from the iodide with moist silver oxide, decomposes when heated into water, and a mixture of two unsaturated bases, methylated on the nitrogen, $C_{15}H_{25}N_2CH_3$, *α-methylsparteine*, m.p. 31°, and *β-methylsparteine*, liquid. The α-methylsparteine hydrohalides isomerize under various conditions to the methyl halide addition compounds of a new base, *isosparteine*, $C_{15}H_{26}N_2$; the methylisosparteinium hydroxide loses water when heated, and forms α-methylsparteine. These reactions, which are analogous to the conversion of methylpiperidine to dimethylpyrrolidine (p. 49), indicate the presence of at least one pyridine ring in sparteine (*Blaise*, *Maire*, Bull. [4] **3**, 674; *Valeur*, *ibid.*, **5**, 31). By exhaustive methylation *Karrer* eliminated both of the nitrogen atoms from sparteine and obtained, by hydrogenation of the resulting unsaturated hydrocarbons, a *pentadecane*, $C_{15}H_{32}$, b.p. 242° (*Karrer*, *Shibata*, *Wettstein*, *Jacubowicz*, Helv. **13**, 1292). For the rupture of the sparteine ring system by cyanogen bromide, see *Winterfeld*, *Ipsen*, Arch.Pharm. **268** (1930), 372. For proposed structures of sparteine, see *Wolffenstein*, *Reitmann*, Biochem. Z. **186** (1927), 269; *Karrer*, *Canal*, *Zohner*, *Widmer*, Helv. **11**, 1068; *Karrer*, *Shibata*, *Wettstein*, *Jacubowicz*, Helv. **13**, 1292; *Winterfeld*, *Kneuer*, Ber. **64**, 152.

A group of alkaloids closely related to sparteine are found in the lupines: **Lupinine**, $C_{10}H_{19}ON$, m.p. 68°, $[\alpha]_D$ −19°; hydrochloride, m.p. 213°, $[\alpha]_D$ −14°, from *Lupinus luteus* and *Lupinus niger* (together with sparteine). **Lupanine**, $C_{15}H_{24}ON_2$, m.p. 44°, $[\alpha]_D$ +51.2°, in *L. albus* and *L. angustifolius*. **Hydroxylupanine**, $C_{15}H_{24}O_2N_2$, m.p. 174° (anhydrous), from *L. polyphyllus*; it can be converted to lupanine with hydriodic acid.

Of these, only lupinine has been investigated for the determination of its structure. It contains a primary alcohol group, which is combined with an asymmetric carbon atom; the tertiary nitrogen atom is shared by three rings (*Schöpf*, Ann. **465**, 97). Anhydrolupinine, resulting from the elimination of water (*Wills*, *Fourneau*, Ber. **35**, 1916), is converted by catalytic hydrogenation to two stereoisomeric lupinanes, $C_{10}H_{19}N$. Oxidation with CrO_3 gives two diastereomeric lupinic acids (*Schöpf*, Ann. **465**, 108), one of which ($[\alpha]_D$ +54.8°, hydrochloride, m.p. 235°) yields on reduction of its ester lupinine (m.p. 68°, $[\alpha]_D$ −23.5°), and the other ($[\alpha]_D$ −19.4°, hydrochloride, m.p. 275°), the isomeric **epilupinine** (m.p. 78°, $[\alpha]_D$ 38.2°)(*Winterfeld, Holschneider*, Ber. **64**, 141). According to *Karrer* (Helv. **11**, 1062), the accompanying formula (I) accounts best for these reactions of lupinine. This structure is further supported by the following experimental results. The pyridine base obtained by decomposition of lupinane with cyanogen bromide and subsequent dehydrogenation is oxidized by $KMnO_4$ to 3-methylpyridine-2-carboxylic acid and 2,3-pyridinedicarboxylic acid, and also some 2-*n*-butylpyridine-3-carboxylic acid (*Winterfeld, Holschneider*, Ber. **64**, 137). That the tertiary nitrogen is in the β-position to the primary alcohol group is proved by the *Hofmann* decomposition of the ketone, $(C_9H_{16}N)\text{-}COC_6H_5$, b.p. 126-128° (1 mm.), picrate m.p. 185°, from lupinic acid ester and phenylmagnesium bromide (*Schöpf*, Ann. **465**, 130), to the unsaturated N-methyl-des-base, $C_{17}H_{23}ON$ (b.p. 143–145° (1 mm.), picrate m.p. 143°) (*Schöpf, Schmidt, Braun*, Ber. **64**, 683).



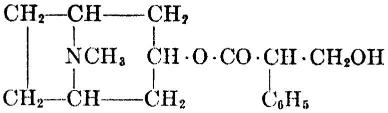
(I)

Lupanine, whose carbon skeleton is joined by two tertiary N-atoms and which contains a carbonyl group, reacts as a monoacid base, due to the presence of a lactam link $=N-CO-$. Energetic reduction with HI and phosphorus converts it first to desoxylupanine, $C_{15}H_{26}N_2$, b.p. 145° (5 mm.), then to β-lupinane, $C_{10}H_{19}N$, b.p. 85-86° (15 mm.), gold salt m.p. 144°, and a base, b.p. 145–147° (15 mm.), which shows pyrrole reactions (*Winterfeld, Kneuer*, Ber. **64**, 150).

III. TROPANE ALKALOIDS

SOLANUM BASES. Many varieties of *Solanum* contain several very similar alkaloids, of which the best known are the two isomers: optically inactive **atropine**, discovered in 1833 by *Meiǹ* and also by *Geiger* and *Hesse*, and its levorotatory form, **hyoscyamine.** When introduced into the eye in very small quantities, they cause the pupil to dilate, and are therefore used medicinally as *mydriatics.* Both bases are found in henbane leaves, *Hyoscyamus niger* and *H. albus*, in the thornapple, *Datura stramonium*, in the "deadly nightshade," *Atropa belladonna*, and in *Duboisia myoporoides;* hyoscyamine also occurs in the *mandragŏra* root (*Thoms, Wentzel*, Ber. **31**, 2031). Associated with these two are many lesser known alkaloids: **belladonine** (p. 341) (*Ladenburg, Roth*, Ber. **17**, 142; *Merling*, Ber. **17**, 383), **hyoscine** = *l*-**scopolamine, atroscine** = *i*-**scopolamine** [*Schmidt*, Ber. **25**, 2601; Ber. **29**, 2009; Arch. Pharm. **247** (1909), 79; *Hesse*, Ber. **29**, 1771, 2439; *Gadamer*, Arch. Pharm. **236** (1898), 382], **apoatropine** (p. 341) [*Merck*, Arch.Pharm. **230** (1892), 134; **231**, 110], these all yield as acid decomposition products tropic or atropic acid, and, as basic constituents, tropine or related compounds. For the isolation of the alkaloids from the plants, see *Chemnitius*, J.pr. **116**, 276 ff.

ATROPINE, inactive **HYOSCYAMINE,** $C_{17}H_{23}O_3N$, m.p. 118°. It is obtained from the plant in an optically inactive form; this is



Atropine

probably due to racemization during the isolation. Atropine can be decomposed by means of its *d*-camphorsulfonate into *d*- and *l*-**hyoscyamine,** m.p. 108°, $[\alpha]_D$—22° (*Barrowcliff, Tutin,* J. **95,** 1966); the latter is probably the only product of the plant synthesis, and its racemization takes place on fusion or on treatment with aqueous or alcoholic sodium hydroxide [*Will,* Ber. **21, 1717**; *Will, Bredig,* Ber. **21,** 2777; *Ladenburg,* Ber. **21,** 3069; *Gadamer,* Arch. Pharm. **239** (1901), 294].

Small quantities of **norhyoscyamine,** $C_{16}H_{21}O_3N$, m.p. 140°, $[\alpha]_D$ −23° (50% alcohol), are often found with hyoscyamine; it is the corresponding methyl-free base.

Atropine (A) salts: sulfate, $2A \cdot H_2SO_4 \cdot H_2O$, m.p. 194°; hydrobromide, $A \cdot HBr$, m.p. 164°; platinum salt, $2A \cdot H_2PtCl_6$, m.p. 208°

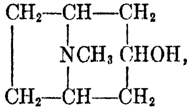
l-Hyoscyamine (Hy) salts: sulfate, $(Hy)_2 \cdot H_2SO_4 \cdot H_2O$, m.p. 206° (anhydrous); hydrobromide, $(Hy) \cdot HBr$, m.p. 151°.

Constitution of Atropine.—When heated with hydrochloric acid or barium hydroxide solution, atropine decomposes into an amino alcohol, the inactive tropine (see below) and *dl*-tropic acid, α-phenylhydracrylic acid, $CH_2OH \cdot CH \cdot (C_6H_5) \cdot COOH$. This reaction can be reversed, atropine being formed by evaporation of tropic acid and tropine with dilute hydrochloric acid (*Ladenburg*), or by condensation of tropine with acetyltropic acid chloride and subsequent elimination of the acetyl group (*Wolffenstein, Mamlock,* Ber. **41,** 726). *l*-Hyoscyamine splits into tropine and *l*-tropic acid when saponified with water, and can be synthesized from these components by evaporation with dilute hydrochloric acid [*Amenomiya,* Arch.Pharm. **240** (1902), 498].

Apoatropine, *atropamine,* $C_{17}H_{21}O_2N$, m.p. 60-62°, is the anhydroatropine, formed from atropine by treatment with nitric acid; it is synthesized by evaporation of tropine atropate with dilute hydrochloric acid. In barium hydroxide solution apoatropine decomposes into tropine and atropic acid (α-phenylacrylic acid: Vol. III, p. 470). It is the *tropeine* of atropic acid.

Belladonine, $C_{17}H_{21}O_2N$, not crystalline (platinum chloride compound, m.p. 229°, amorphous). This base is a stereoisomer of *atropamine,* and is obtained from the latter by heating alone or by evaporating with hydrochloric acid. In the latter case saponification to atropic acid and *bellatropine,* an isomer of tropine, also occurs.

TROPEINES. Tropeines are ester-like compounds obtained from tropine with other acids, as atropine is formed from tropine with tropic acid (*Ladenburg,* Ann. **217,** 82; *Petit, Polonowsky,* Bull. [3] **9,** 1015). **Homatropine,** phenylglycolyltropeine, $C_8H_{14}N(O \cdot CO \cdot CHOH \cdot C_6H_5)$, m.p. 95-98.5°, is prepared from tropine and mandelic acid; because its mydriatic action is not so prolonged, it is used in the form of its hydrobromide in place of atropine. Only those tropeines having an alcoholic hydroxyl group in their acyl radical show pronounced mydriatic action (for this relationship, see *Pyman,* J. **111,** 1103). *Lactyltropeine,* m.p. 74° (Ger. Pat. 79870, 1894). *Benzilotropeine,* the tropeine of benzilic acid (*Petit, Polonowsky,* Bull. [3] **9,** 1015).

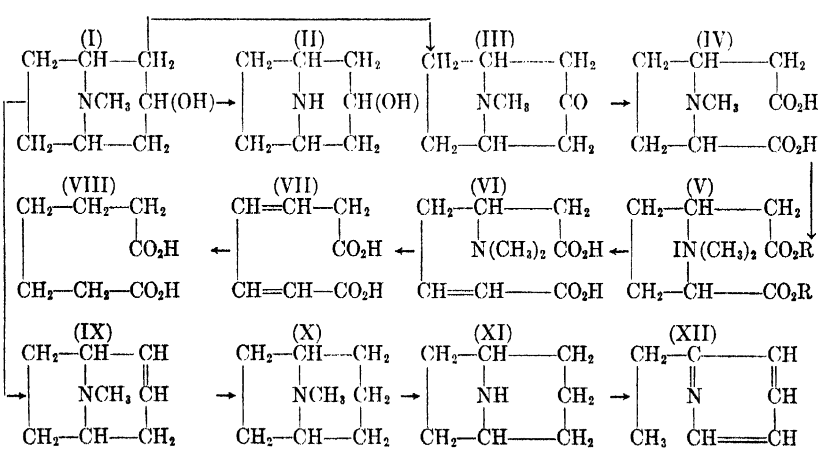
Tropine, $C_8H_{15}ON$,  m.p., 62°, b.p. 333°, the basic decomposition product of atropine, was found by *Willstätter* to have a bicyclic ring system comprising a pyrrolidine ring condensed with a 4-hydroxypyridine ring, the group C—N—C being common to the two rings (see also p. 270).

The principal evidence for the above structure for tropine is the formation of a *dibenzylidene* and a *diisonitroso compound* from *tropinone*, the first oxidation product of tropine, which signifies that tropinone must contain the group $—CH_2·CO·CH_2—$ (*Willstätter*, Ber. **31**, 1537).

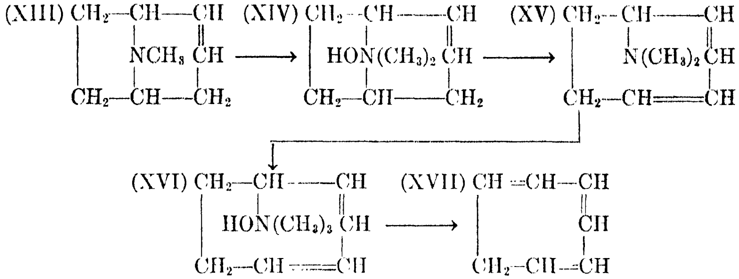
The constitution of tropine and ecgonine is clarified also by their decomposition reactions, especially the *Hofmann* exhaustive methylation method. These data are due to the work of *Ladenburg*, *Merling*, *Einhorn*, *Willstätter*. The formulas so obtained are verified by the syntheses of these compounds.

Decomposition of Tropine.—(Equations shown below.) (*a*) *The conversion of tropine into tropic acid and n-pimelic acid:* Tropine (I) is oxidized by $KMnO_4$ in alkaline solution to tropigenine (II), and in acid solution, or with chromic acid, to tropinone (III), a ketone, which gives tropine when reduced with zinc dust and hydriodic acid, but with other reducing agents yields the stereoisomeric ψ-tropine, which is also obtained from a subsidiary alkaloid of cocaine (p. 344) (*Willstätter*, *Iglauer*, Ber. **33**, 1170). Further oxidation with CrO_3 converts tropinone to tropinic acid (IV), 5-carboxy-1-methyl-2-pyrrolidineacetic acid. The methyl iodide addition product of tropinic acid ester (V) is split by alkali to the so-called methyltropinic acid (VI), whose methyl iodide, treated with alkali, gives piperylenedicarboxylic acid (VII); by reduction of the latter *n*-pimelic acid (VIII) is obtained. Therefore the presence of 7 carbon atoms in a row in the tropine molecule is proved.

(*b*) The conversion of tropine to 2-ethylpyridine and picolinic acid: By elimination of water by means of glacial acetic acid and hydrochloric acid tropine is converted to tropidine (IX), which is oxidized by permanganate to dihydroxytropidine; on further oxidation the latter yields tropinic acid (IV) (*Willstätter*, Ber. **28**, 2277). Zinc and hydrochloric acid reduce tropidine to hydrotropidine, tropane (X), which is also obtainable from tropinone (III) (*Willstätter*, *Iglauer*, Ber. **33**, 1173). Norhydrotropidine (XI) is formed by heating tropane hydrochloride in a stream of hydrogen chloride and is distilled over zinc dust to give 2-ethylpyridine (XII), which yields picolinic acid on oxidation (*Ladenburg*, Ber. **20**, 1647).

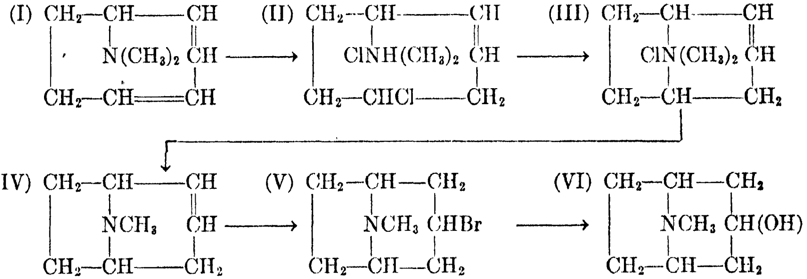


(*c*) *The conversion of tropidine to tropilidene or* 1,3,5-*cycloheptatriene* (see *Willstätter*, Ber. **31**, 1542): Tropidine (XIII) adds methyl iodide, and the product is converted by moist silver oxide to methyltropidinium hydroxide (XIV), which rearranges in boiling water to "methyltropidine" or 5-dimethylamino-1,3-cycloheptadiene (XV). The latter, subjected to the same treatment as tropidine, yields the trimethylammonium hydroxide (XVI) and tropilidene, 1,3,5-cycloheptatriene (XVII):



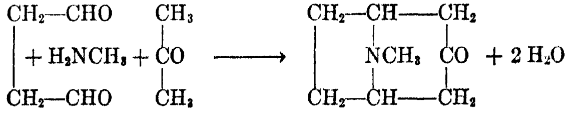
Hydrotropidine is similarly converted to cycloheptadiene. *Tropilene*, $C_7H_{11}O$, 2-*cyclohepten*-1-*one*, formed by the exhaustive methylation of tropidine, can be catalytically hydrogenated to cycloheptanone (*Kötz*, *Rosenbusch*, Ber. **44**, 464).

Synthesis of Tropine.—"Methyltropidine" or 5-dimethylamino-1,3-cycloheptadiene (I) forms 6-chloro-3-dimethylamino-1-cycloheptene hydrochloride (II) by addition of 2 HCl; elimination of 1 HCl with aqueous sodium hydroxide converts this to methyltropidinium chloride (III), which decomposes when it is dist. into tropidine (IV) and methyl chloride. Tropidine adds HBr to give 3-bromotropane (V), from which tropine (VI) is obtained with dilute mineral acid (*Willstätter*, Ann. **326**, 1).



By analogous reactions, tropane (p. **342**) is produced from "methyltropane," dimethylaminocycloheptene. These syntheses have been completed by the formation of "methyltropidine" and "methyltropane" from 1,3,5-cycloheptatriene (tropilidene) and cycloheptene, which are obtainable from the synthetic suberone, cycloheptanone (*Willstätter*, Ber. **34**, 129; Ann. **317**, 307).

The synthesis of the tropane ring system developed by *Robinson* (J. **111**, 762) is much simpler. *Succinaldehyde*, *methylamine*, and *acetone* in aqueous solution form detectable amounts of *tropinone* in a short time:

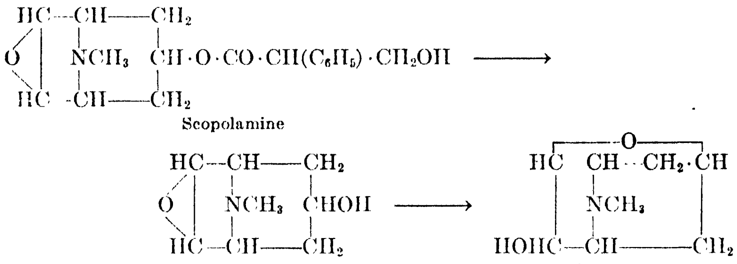


The yields are considerably larger when β-ketoglutaric acid ester is used in place of acetone, the tropinone-dicarboxylic acid first formed being readily decarboxylated to tropanone. By use of the monoethyl ester of β-ketoglutaric acid, this reaction is suitable for the direct preparation of *ecgonine* (see page 345).

l-Scopolamine (*hyoscine*), $C_{17}H_{21}O_4N$ (formula given below), syrup, $[\alpha]_D$

−28° (water), hydrobromide, scop·HBr·3 H_2O, m.p. 193° (anhydrous), is associated in many plants with *l-hyoscyamine*, from whose mother liquor it is usually obtained. **Atroscine** (dihydrate, m.p. 38–40°; monohydrate, m.p. 56°) is inactive scopolamine. *d-Scopolamine*, $[\alpha]_D$ +26.3°, prepared by resolution of the inactive scopolamine (*King*, J. **115**, 476).

These alkaloids are related to hyoscyamine. Scopolamine is the tropic acid ester of *scopine*, $C_8H_{13}O_2N$, m.p. 76°, an amino alcohol analogous to tropine. Scopine is obtainable from scopolamine only by very mild, alkaline hydrolysis (ammonia plus ammonium chloride at *p*H 8.9–9) (*Willstätter*, *Berner*, Ber. **56**, 1079). When warmed alone, or more rapidly in the presence of alkali, scopine rearranges to scopoline, m.p. 109°, b.p. 241–243°, an ethylene oxide ring being converted to a butylene oxide ring (*Hess*, *Wahl*, Ber. **55**, 1979; *Willstätter*, *Berner*, Ber. **56**, 1079). This reaction had long concealed the true constitution of scopolamine.


Scopolamine

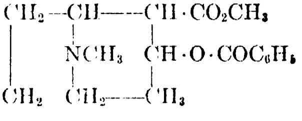
Scopine

Scopoline

When scopoline is heated with saturated glacial acetic acid–hydrobromic acid at 100°, the oxide ring is broken and the hydrobromide of a hydrobromoscopoline is formed (*Hess*, *Suchier*, Ber. **48**, 2060). This reduces to *dihydroscopoline*, a 6,7-dihydroxytropane, which yields *scopolinic acid*, *1-methylpiperidine-2,6-dicarboxylic acid*, m.p. 230° (anhydrous), on stronger oxidation (*Hess*, *Suchier*, Ber. **48**, 2061). Reduction with hydriodic acid and phosphonium iodide converts dihydroscopoline to *tropane*, a reaction which places scopoline in the bicyclic tropane group (*Hess*, Ber. **51**, 1008). For the products of the exhaustive methylation of methylscopoline iodide, see *Hess*, Ber. **52**, 1947.

Scopolamine is used for the induction of twilight sleep in gynecology and for the relief of cramps of the bile duct musculature.

l-COCAINE, $C_{17}H_{21}O_4N$,



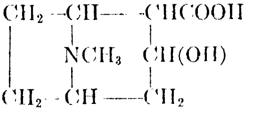
m.p. 98°, $[\alpha]_D$ −15.8°, hydrochloride m.p. 200° (anhydrous), $[\alpha]_D$ −71.9° (in water), is found in the leaves of *Erythroxylon coca.* [Production on a technical scale: *Duilius*, Chem.Ztg. **54** (1930), 31; *Chemnitius*, J.pr. **116**, 276.] It is used in the form of its hydrochloride as a local anesthetic; large doses are fatal, due mostly to paralysis of the respiratory center. When warmed with hydrochloric acid it decomposes into ecgonine (tropinecarboxylic acid) (p. 345), benzoic acid and methanol, while in boiling water it gives benzoylecgonine and methanol. Conversely, cocaine can be formed from ecgonine, benzoylecgonine and ecgonine methyl ester, either by benzoylating ecgonine methyl ester or by esterifying benzoylecgonine with methanol. Because of this, several other alkaloids of the cocaine group, *cinnamylcocaine* (methylcinnamylecgonine, m.p. 121°) and *truxilline* (methyl-α- and β-truxilloylecgonine) (*Liebermann, Bergami*, Ber. **22**, 783, footnote), are technically valuable, because they yield ecgonine methyl ester and ecgonine on fission (*Sembritzki*, Ber. **22**, 2960).

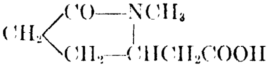
eudococaine, m.p. 43–45° (hydrochloride, m.p. 208°, $[\alpha]_D$ +49.8°, in r), found in small quantity in the mixture of cocaine bases (*Liebermann*, *iesel*, Ber. **23**, 926), has been synthesized from *d*-pseudoecgonine (see below) (*Einhorn, Marquardt*, Ber. **23**, 982; *Willstätter, Wolfes, Mäder*, Ann. **434**, 126). A *l*-**pseudococaine** has also been prepared (*loc. cit.*, p. 125). *dl*-**Cocaine**, m.p., 79–80°, obtained synthetically (see below, and *Willstätter, Bommer*, Ann. **422**, 15; *Willstätter, Wolfes, Mäder*, Ann. **434**, 111). *dl*-**Pseudococaine**, m.p. 81.5°, obtained synthetically (see below, and preceding reference).

Tropacocaine, *benzoyl-ψ-tropine*, $C_{15}H_{19}NO_2$, m.p. 49°, occurs in small amounts in the coca alkaloids. When decomposed it yields benzoic acid and ψ-tropine, m.p. 108°, b.p. 241°, which is a stereoisomer of tropine, since it is also formed by the reduction of tropinone, oxidizes to tropinone and is produced directly from tropine by rearrangement with sodium amylate. Oxidation with $KMnO_4$ converts ψ-tropine to ψ-tropigenine, which, like tropigenine (p. 342), yields nortropinone when oxidized (*Willstätter*, Ber. **29**, 936, 1636, 2231; *Barrowcliff, Tutin*, J. **95**, 1966). It also acts as a local anesthetic.

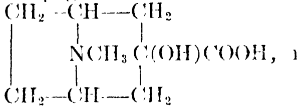
Crude cocaine contains small amounts of **hygrine**, $C_8H_{15}ON$, b.p. 92–94° (20 mm.), which is 1-methyl-2-acetonylpyrrolidine (see p. 330).

l-**Ecgonine** (I), *tropinecarboxylic acid*, $C_9H_{15}O_3N \cdot H_2O$, m.p. 205° (anhydrous), $[\alpha]_D$ −45.4°, is the basic decomposition product of *l*-cocaine. Methyl ester: hydrochloride m.p. 212° (dec.). Warming with aqueous potassium hydroxide converts *l*-ecgonine to *d*-ψ-**ecgonine**, m.p. 254°. For esters, amides, and nitriles of the ecgonines, see *Deckers, Einhorn*, Ber. **24**, 7; *Einhorn, de Norwall*, Ber. **26**, 962; for the alkyl iodide addition products, see *Hesse*, J.pr. **65**, 91. Both *l*- and *d*-ecgonine are oxidized by CrO_3 to *l*-ecgoninic acid, 1-methyl-5-oxo-2-pyrrolidine-acetic acid (II), m.p. 117°, whose racemic form, m.p. 94°, is obtained together with tropinic acid (p. 50) by the oxidation of tropine with CrO_3, and, synthetically, from β-bromoadipic acid with methylamine (*Willstätter, Hollander*, Ber. **34**, 1818). For other decomposition products of ecgonine, see the reaction scheme on p. **346**.

(I) 

 (II)

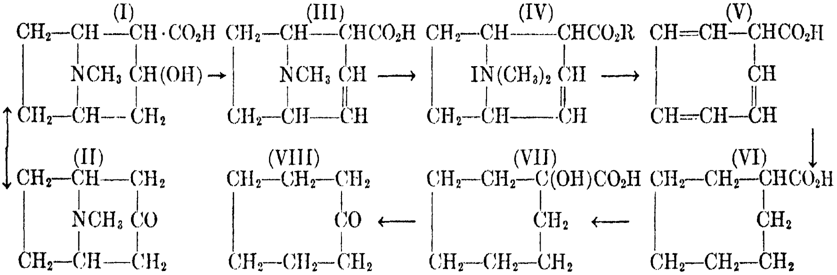
dl-**Ecgonine**, see page 346.

α-**Ecgonine**,  m.p. 305° (dec.), an isomer of ecgonine, has been prepared by adding hydrocyanic acid to tropinone (p. 342) and saponifying the cyanohydrin (*Willstätter*, Ber. **29**, 2216).

Anhydroecgonine, $C_9H_{13}NO_2$, m.p. 234° (formula III in the diagram below), is formed from ecgonine hydrochloride by boiling with phosphorus oxychloride (*Einhorn*, Ber. **20**, 1221). Reduction converts it to **hydroecgonidine**, $C_9H_{15}NO_2$, m.p. 200°.

The relation of ecgonine to tropine is evident from the rearrangement of anhydroecgonine when heated with hydrochloric acid at 280° (with simultaneous decarboxylation) to tropidine, which was first observed by *Einhorn* (Ber. **23**, 1338). Tropidine is also obtained by reacting hydroecgonine amide, $(C_8H_{14}N)$-$CONH_2$, with KOBr and treating the **isotropylamine**, $(C_8H_{14}N)NH_2$, so formed with nitrous acid (*Willstätter, Müller*, Ber. **31**, 2655).

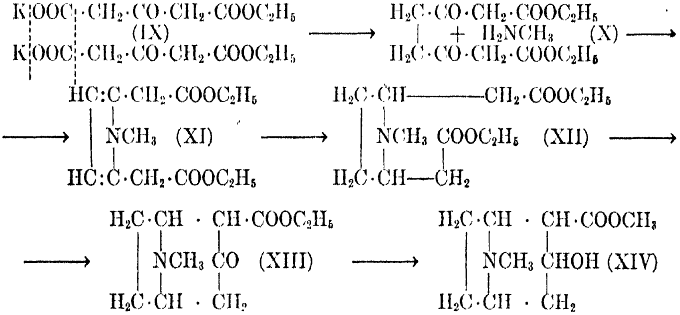
Decomposition of Ecgonine.—Conversion of ecgonine to tropinone and *cycloheptanone*: The position of the carboxyl group in the tropane ring of ecgonine (I) is indicated by the oxidation to tropinone (II) with chromic acid, since the loss of CO_2 is characteristic of the oxidation of β-hydroxycarboxylic acids (*Willstätter*, *Müller*, Ber. **31**, 2655). If anhydroecgonine (III) (see below) is esterified and treated with methyl iodide, a methyl iodide addition product (IV) is formed. This is converted by moist silver oxide to anhydroecgonine methylbetaine, which is decomposed by boiling with alkali to dimethylamine and tropilidenecarboxylic acid, 2,4,6-cycloheptatriene-1-carboxylic acid (V), m.p. 32° (amide, m.p. 125°). The constitution of the latter is known from its reduction to cycloheptanecarboxylic acid (VI) and the conversion of the latter through the bromo or hydroxy derivative (VII) to cycloheptanone (VIII) (*Willstätter*, Ber. **31**, 2498):



By a similar series of reactions, hydroecgonidine is converted to hydrotropilidenecarboxylic acid, cycloheptadienecarboxylic acid (*Willstätter*, Ber. **30**, 702; **31**, 2501).

Synthesis of Ecgonine.—The conversion of ecgonine to tropinone (II), which constitutes a new transition from cocaine to atropine, is reversed by the synthesis of ecgonine from tropinone. Tropinone (p. 342), obtained from tropine, is partially converted to racemic ecgonine by treatment with Na and CO_2 (*Willstätter, Bode*, Ber. **34**, 1457).

Willstätter and his coworkers (*Willstätter, Pfannenstiel*, Ann. **422**, 1; *Willstätter, Bommer, ibid.*, 15) have developed a simpler synthesis for *dl*-ecgonine, and thereby for cocaine, starting from β-oxoglutaric acid. The *potassium salt* of the *ethyl ester* of this acid (IX) is converted electrochemically to *β,ε-dioxosuberic acid ester* (X), which, being a 1,4-diketone, reacts with methylamine to give 1-*methyl-2,5-pyrrolediacetic ester* (XI). This is catalytically hydrogenated (Pt + H_2) to the corresponding pyrrolidine derivative (XII), which undergoes an intramolecular acetoacetic ester condensation, forming *tropinonecarboxylic acid ethyl ester* (XIII) (which is also obtained from tropinone by partial synthesis, see above). This can be reduced to *ecgonine ethyl ester*, which, after transformation to the methyl ester (XIV), can be benzoylated to *dl-ψ-cocaine:*



Another synthesis introduced by *Willstätter* and his coworkers (*Willstätter, Wolfes, Mäder*, Ann. **434**, 111) is based on the preparation of methyl tropinonecarboxylate given on p. 343. When the preparation is conducted on a large scale, reduction of the ester yields three racemic ecgonines. The following outline shows the compounds so produced and the cocaines obtainable from them:

I. *dl*-ψ-Ecgonine methyl ester, m.p. 128° $\xrightarrow{\text{benzoylation}}$ *dl*-ψ-Cocaine, m.p. 81.5°

dl-ψ-Ecgonine methyl ester, m.p. 128° $\xrightarrow{\text{resolvable}}$

- *d*-ψ-Ecgonine methyl ester, m.p. 116°, $[\alpha]_D$ + 19.5° (water) (*loc. cit.*, p. 124) $\xrightarrow{\text{benzoylation}}$ *d*-ψ-Cocaine (natural *d*-cocaine)
- *l*-ψ-Ecgonine methyl ester, m.p. 115°, $[\alpha]_D$ −14.7° (methanol)

↑ rearrangement by alkali

II. *dl*-Ecgonine methyl ester: hydrochloride, m.p. 195° $\xrightarrow{\text{benzoylated}}$ *dl*-Cocaine, m.p. 79–80° $\xrightarrow{\text{resolvable}}$

- *d*-Cocaine, m.p. 98°, $[\alpha]_D$ +15.8° (*loc. cit.*, p. 132)
- *l*-Cocaine, m.p. 98°, $[\alpha]_D$ −16.5° (natural *l*-cocaine)

III. *dl*-Ecgonine (by hydrolysis of the methyl ester), m.p. 225° (anhydrous), not resolved up to the present time (*loc. cit.*, p. 114)

The Spatial Configuration of Ecgonine

A comprehensive theoretical explanation of the spatial relations in the tropane system has been devised to include the numerous racemic and optically active ecgonines and cocaines, not all of which are synthesized by the plant (*Willstätter, Bommer,* Ann. **422,** 18). This bicyclic ring system may be considered to consist of three segments, whose planes intersect in the line of the bond between the two CH-groups (Fig. 1). If this line is placed at right angles to the plane of the paper, then Figure 2 represents the projection of the three tropane segments on that plane.

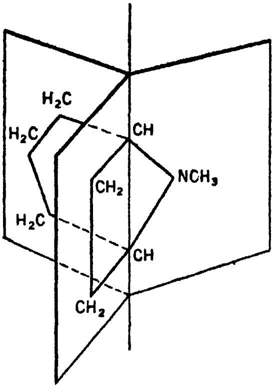


Figure 1. Tropane.

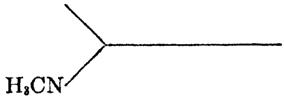
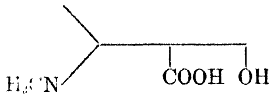
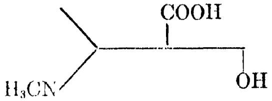


Figure 2.

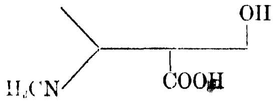
Substitution in the 3-position of tropane (tropines) should give two *cis-trans* isomeric tropines. If a carboxyl group is also substituted in the 2-position (ecgonines), then for each of these tropines there are two *cis-trans* isomeric ecgonines, which, because of the asymmetry conditioned by the entrance of the COOH—group in the 2-position, give racemic modifications. There are therefore four racemates of



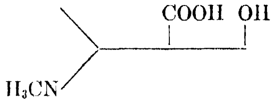
Tropane-3 *cis*-ol-2 *cis*-
carboxylic acid



Tropane-3 *cis*-ol-2 *trans*-
carboxylic acid



Tropane-3 *trans*-ol-2 *cis*-
carboxylic acid

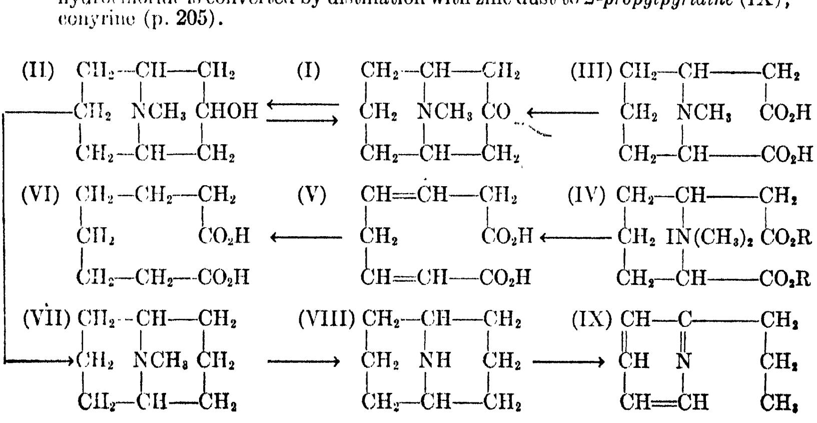


Tropane-3 *trans*-ol-2 *trans*-
carboxylic acid

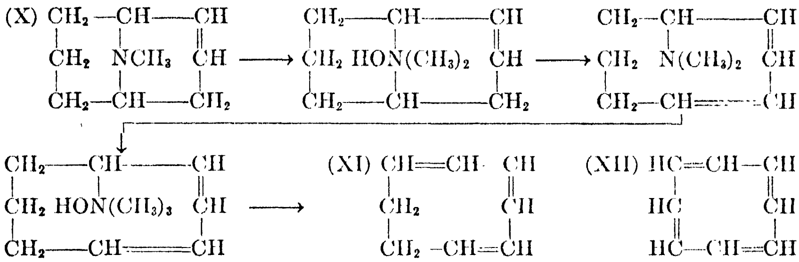
ecgonine, which are illustrated by the accompanying schematic formulas (*cis*- and *trans*- refer to the relation to the nitrogen segment). Of these, three are known. One belongs to the series of natural cocaine, a second to ψ-cocaine.

The principal alkaloid of the pomegranate root bark (*Punica granatum*) is pseudopelletierine, discovered by *Tanret* (1879) and named after the Frenchman *Pelletier*. From their reactions, most of which were investigated by *Ciamician* and *Silber* (Ber. **25**, 1601; **26**, 156, 2740), they appear to be similar in structure to the tropane alkaloids. In their natural occurrence they are associated with a series of monocyclic alkaloids, which have been treated on p. 335.

PSEUDOPELLETIERINE, *methylgranatonine*, $C_9H_{15}ON$ (I), m.p. 48°, b.p. 246°, optically inactive, is a ring homologue of tropinone (p. 342), and, like it, forms a dibenzylidene and a diisonitroso derivative, indicating the presence of the group —$CH_2 \cdot CO \cdot CH_2$— [*Piccinini*, Atti accad.Lincei [5] 8 (1899), I, 392]. On reduction it gives the alkamine corresponding to ψ-tropine, ψ-methylgranatoline (II) (in electrolytic reduction the stereoisomeric methylgranatoline is also formed), which is oxidized by chromic acid first to pseudopelletierine and then to methylgranatic acid (III), analogous to tropinic acid (p. 50). Methylgranatic acid has been converted by exhaustive methylation to suberic acid: the methyl iodide of methylgranatic acid ester (IV) is split by alkali to the so-called dimethylgranatic acid, whose methyl iodide yields with alkali homopiperylenic acid (V); this reduces with sodium amalgam to *suberic acid* (VI). With HI and phosphorus, methylgranatoline is reduced to methylgranatanine (VII) [which is also obtained directly from methylgranatonine (I) by electrolytic reduction: *Willstätter, Veraguth*, Ber. **38**, 1986] and granatanine (VIII). Granatanine hydrochloride is converted by distillation with zinc dust to 2-*propylpyridine* (IX), conyrine (p. 205).



By elimination of water from methylgranatoline with glacial acetic acid and concentrated H_2SO_4, methylgranatenine (X) is formed; as tropidine gives cycloheptatriene, so this is converted by exhaustive methylation to *cycloöctatriene* (XI). *Willstätter* was able to introduce another double bond into this triene by means of the dibromide, and so obtained the interesting ring homologue of benzene, *cycloöctatetraene* (XII), a yellow oil (*Willstätter, Waser*, Ber. **44**, 3423; *Willstätter, Heidelberger*, Ber. **46**, 517).



By this method methylgranatanine gives 1,5-cycloöctadiene. Under somewhat different conditions, methylgranatenine decomposes to granatal, $C_8H_{12}O$, 3-cyclooctenone, the analogue of tropilene (p. 343) [*Ciamician, Silber*, Ber. **29**, 481; *Willstätter, Veraguth*, Ber. **38**, 1975; *Willstätter, Waser*, Ber. **44**, 3423; *Piccinini*, Gazz. **29** (1899), II, 104; Atti accad.Lincei [5] **8** (1900), II, 219; *Piccinini, Quartaroli*, Gazz. **29** (1899), II, 115].

IV. ALKALOIDS OF THE QUINOLINE GROUP

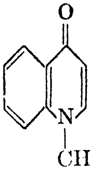
CYTISINE, *ulexine*, *sophorine*, $C_{11}H_{14}N_2O$, m.p. 152°, b.p. 218° (2 mm.), occurs in the seeds of *Cytisus laburnum* and other varieties of *Cytisus*, and of *Sophora tomentosa* and *speciosa* [*Parthiel*, Ber. **23**, 3201; **24**, 634; Arch.Pharm. **232** (1894), 161; *Plugge*, Arch.Pharm. **232** (1894), 444, 557; **233** (1895), 430; *Gortner*, Arch.Pharm. **233** (1895), 527; *Rauwerda*, Nederl.Tydschr.Pharm. **12** (1900), 161]. Cytisine contains an imino group: *acetyl derivative*, m.p. 174°, *benzoyl derivative* m.p. 116°. With concentrated nitric acid it gives a *nitronitrosocytisine*, from which the nitroso group can be eliminated, leaving *nitrocytisine*, which can be reduced to *aminocytisine*. With hydrogen peroxide it is oxidized to *hydroxycytisine*, $C_{11}H_{14}N_2O_2$. Reduction with HI and phosphorus yields, among other products, *cytisoline*, $C_{11}H_{11}ON$, m.p. 199° (see below), which is oxidized by CrO_3 to *cytisolinic acid*, $C_{11}H_9NO_3$, and reduced by Na and alcohol to *α-cytisolidine*, $C_{11}H_{15}N$ (platinum chloride, m.p. 216°). When reduced electrolytically cytisine gives a base $C_{11}H_{22}N_2$ (*Freund, Horkheimer*, Ber. **39**, 818).

Knowledge of the constitution of cytisine has been gained mostly from the reduction products with hydriodic acid. *Cytisoline*, $C_{11}H_{11}ON$, has been proved by synthesis to be 6,8-*dimethyl-2-quinolinol* (*Späth*, Mo. **40**, 93); the *α-cytisolidine*, $C_{11}H_{15}N$, obtained from it by reduction is 6,8-*dimethyl*-1,2,3,4-*tetrahydroquinoline* (*Ewins*, J. **103**, 103). Therefore cytisine is certainly a quinoline derivative. Its exact constitution is not known (*cf. Späth*, Mo. **40**, 15, 93). For proposed formulas, see *Späth*, Z.angew.Chem. **1928**, 1260.

Anagyrine, $C_{15}H_{22}N_2O$ (?), which is closely related to cytisine, is found with it in the seeds of *Anagyris foetida* [*Schmidt*, Arch.Pharm. **238** (1900), 184].

The alkaloids which are derivatives of 4-quinolinol are similar in structure to the 4-pyrone or chromone compounds, which are also often produced by plant syntheses.

Echinopsine, $C_{10}H_9ON$, m.p. 152°, a simple alkaloid of this type, is obtained from the seeds of *Echinops ritro*. It is 1-methyl-4-quinolone:



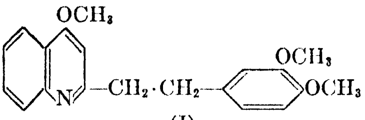
This structure is supported by its conversion with PCl_5 to 4-chloroquinoline and its reduction with Na and alcohol to 1-methyltetrahydroquinoline (*Späth, Kolbe*, Mo. **43**, 469).

The following alkaloids, which are almost as simple in constitution, occur in the angostura bark (*Galipea cusparia*), which is native to South America:

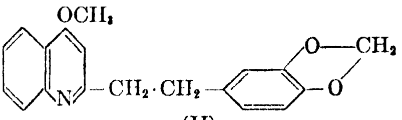
Galipine (I), $C_{20}H_{21}O_3N$, m.p. 113.5°, and **cusparine** (II), $C_{19}H_{17}O_3N$, m.p. 92° (isolation from the bark: *Späth, Eberstaller*, Ber. **57**, 1689).

Galipoline, $C_{19}H_{19}O_3N$, m.p. 193° (*Späth, Papaioanou*, Mo. **52**, 129).

These are tertiary bases. Galipine contains three methoxy groups, and cusparine contains one. Both bases yield *protocatechuic acid* on alkali fusion. The structure of the second half of the molecule follows from the results of chromic acid oxidation. Galipine gives *4-methoxyquinoline-2-carboxylic acid* [identical with the methyl ether of kynurenic acid (p. 242) and *Späth, Brunner*, Ber. **57**, 1245] and veratric acid.



(I)



(II)

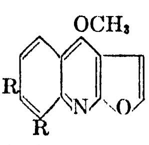
These formulas, deduced from the analytical results, are verified by the synthesis of galipine from 2-methyl-4-methoxyquinoline and veratraldehyde, and of cusparine from 2-methyl-4-methoxyquinoline and piperonal, the unsaturated bases first formed being reduced (*Späth, Brunner*, Ber. **57**, 1243; *Späth, Eberstaller*, Ber. **57**, 1687). Galipoline has a free OH-group in the 4-position of the quinoline ring. It can be converted to galipine by methylation.

In the group of *skimmia* alkaloids there are several naturally occuring substances which contain a quinoline ring fused with a furan ring. Their structure is known through their oxidative decomposition to quinoline derivatives of known constitution by *Asahina*.

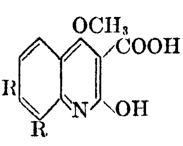
Skimmianine, $C_{14}H_{13}O_4N$, m.p. 176°, is obtained from the leaves of *Skimmia japonica*. This compound contains an ether-like oxygen atom and three methoxy groups, of which one isomerizes when treated with CH_3I to an N-methyl-4-quinolone, a reaction typical of 4-methoxyquinolines, while the other two are evidently *ortho* to one another.

The oxidation of skimmianine with $KMnO_4$ yields the aldehyde *skimmianal*, $C_{13}H_{13}O_5N$ (m.p. 238°), containing one less carbon atom, and the corresponding *skimmianic acid*, $C_{13}H_{13}O_6N$ (m.p. 248°), which is converted by decarboxylation and partial demethylation to *7,8-dimethoxy-2,4-quinolinediol* (m.p. 250°). These experimental results are best expressed by (III) for skimmianine and (IV) for the acid decomposition product (*Asahina, Nakanishi*, Ber. **63**, 2057):

(III)



Skimmianine (R = OCH_3)
Dictamnine (R = H)



(IV)

Skimmianic acid (R = OCH_3)
Dictamnic acid (R = H)

Dictamnine, $C_{12}H_9O_2N$, m.p. 132°, occurs in the leaves of *Skimmia repens* and in the root of *Dictamnus*. Its constitution as the methoxy-free analogue of skimmianine follows from analogous decomposition reactions (*Asahina, Ohta, Inubuse*, Ber. **63**, 2045).

V. QUINOLINE-QUINUCLIDINE GROUP: CINCHONA ALKALOIDS

Cinchona barks (*cortex chinae*) are derived from various Cinchona species, native to Bolivia and Peru and now also cultivated in Java: *Cinchona calisaya, C. lancifolia, C. pitayensis* and *rubiaceen.* They contain, in addition to tannin, a bitter principle, *quinovine* (*Wieland, Erlenbach,* Ann. **453,** 83), and *quinic acid,* a series of bases, the most important of which are:

Quinine.........	$C_{20}H_{24}N_2O_2$	Quinidine (conquinine)...	$C_{20}H_{24}N_2O_2$
Cinchonine.....	$C_{19}H_{22}N_2O$	Cinchonidine............	$C_{19}H_{22}N_2O$

Hydrocinchonine, cinchotine, $C_{19}H_{24}N_2O$, is associated with cinchonine (*Hesse,* Ann. **300,** 42; *Arlt,* Mo. **20,** 425), and *cupreine* (p. 352) is associated with quinine.

QUININE, $C_{20}H_{24}N_2O_2 + 3\ H_2O$, m.p. 173° (anhydrous), $[\alpha]_D^{15}$ $-158°$ (alcohol), crystallizes from alcohol and ether in silky needles. Quinine was discovered by *Pelletier* and *Caventou* in 1820; it is one of the most valuable medicinals, especially for intermittent fevers, such as malaria, and is an antidote for many infections produced by microörganisms. It constitutes up to 12% of the yellow calisaya bark. It has an alkaline reaction and a bitter taste, and, being a diacid base, forms primary and secondary salts.

Of these salts the sulfate, $(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4 + 8\ H_2O$, and the hydrochloride, $C_{20}H_{24}N_2O_2 \cdot HCl + 2\ H_2O$, are used medicinally. The former forms long, shiny needles which fall to a white powder when exposed to the air. It dissolves in dilute sulfuric acid, giving a solution with a blue fluorescence.

When a solution of a quinine salt is treated first with chlorine or bromine water and then with ammonia, a green precipitate is formed; this redissolves in excess ammonia with an emerald-green color (thalleioquinic reaction). Alcoholic iodine solution added to the acetic acid solution of the sulfate precipitates herapathite, $4Q \cdot 3\ H_2SO_4 \cdot 2\ HI \cdot I_4 + 3\ H_2O$, which crystallizes in emerald-green plates with a golden luster and polarizes light like tourmaline.

CINCHONINE, $C_{19}H_{22}N_2O$, is associated with quinine; it occurs principally in the grey cinchona bark (*Cinchona huanaco*) (up to 2.5%). It crystallizes from alcohol in white prisms, sublimes in needles in a current of hydrogen and melts at 264°; $[\alpha]_D$ $+229°$ (abs. alcohol). Like quinine it is a febrifuge, but a less effective one.

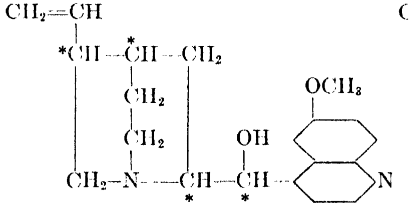
Quinidine, m.p. 171°, $[\alpha]_D$ $+229°$ (abs. alcohol), and **cinchonidine,** m.p. 202°, $[\alpha]_D$ $-111°$, are shown by their reactions (see below) to be stereoisomers of quinine and cinchonine respectively. Cinchonine can be converted to cinchonidine by heating with KOH in amyl alcohol (*Koenigs, Husmann,* Ber. **29,** 2185). For the stereochemistry of the cinchona alkaloids, see *Rabe,* Ann. **373,** 85.

Constitution.—Quinine and cinchonine are unsaturated, ditertiary bases. They form primary and secondary salts, and add one or two molecules of alkyl iodide. The monoalkyl iodides exist in two isomeric forms, one colorless and the other dark yellow; the former is obtained by combining the free base with one molar proportion of alkyl iodide, and the latter by warming the monoiodohydrate with alkyl iodide and then treating with ammonia (*Skraup, v. Norwall*, Ber. **26**, 1968).

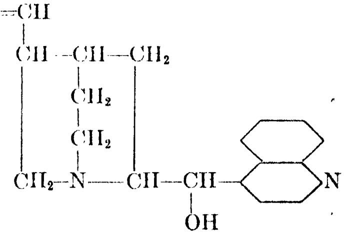
In accordance with their unsaturated structure, quinine and cinchonine add one molecule of hydrogen halide and two atoms of bromine. The dibromides are converted by alkali first to *monobromoquinine* and *monobromocinchonine* and then to *dehydroquinine* and *dehydrocinchonine*, $C_{20}H_{22}N_2O_2$ and $C_{19}H_{20}N_2O$ (*Comstock, Koenigs*, Ber. **19**, 2856; *Christensen*, J.pr. **69**, 193). For the addition of sulfurous acid to quinine and quinidine, see *Koenigs* and *Schönewald*, Ber. **35**, 2980. With hydrogen and colloidal platinum, quinine, quinidine, cinchonine and cinchonidine add 2 atoms of hydrogen to form the bases: *hydroquinine*, m.p. 172° (anhydrous), $[\alpha]_D^{20}$ −142.2°; *hydroquinidine*, m.p. 167°, $[\alpha]_D$ + 230° *hydrocinchonine* (*cinchotine*), m.p. 268°, $[\alpha]_D$ +204.5° (alcohol); and *hydrocinchonidine* (*cinchamidine*), m.p. 229°, $[\alpha]_D$ −98.4° (alcohol). These hydrogenated derivatives have also been found together with quinine and cinchonine in the cinchona barks (*Knorr, Hess*, Ber. **44**, 2866; *Skita*, Ber. **45**, 3317; *Heidelberger, Jacobs*, Am. **41**, 817).

With strong mineral acids the cinchona alkaloids rearrange to isomeric bases: *isoquinine, isoquinidine, isocinchonine*, and *isocinchonidine*. The reaction of hydrohalogen acids with cinchonine at room temperature has been investigated in detail, since both the hydrogen halide addition product of cinchonine and α-isocinchonine are formed simultaneously; the mechanism of this isomerization has been clarified (*Rabe, Böttcher*, Ber. **50**, 127). *α-Isocinchonine* has been identified as the oxide of *hydroxydihydrocinchonine* (see formula) (*Skraup*, Mo. **20**, 571, 585; **22**, 171, 253; *Böttcher, Horowitz*, Mo. **32**, 793).

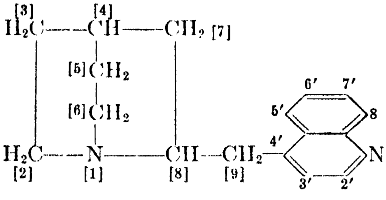
The following formulas for quinine and cinchonine have been firmly established by numerous investigations, by *Koenigs, v. Miller, Rabe, Rohde, Skraup* and others (*Koenigs*, Ann. **347**, 143; *Rabe*, Ann. **350**, 180; **364**, 330; **365**, 353):



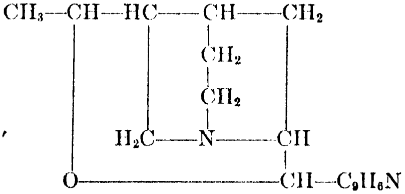
Quinine



Cinchonine



Rubane

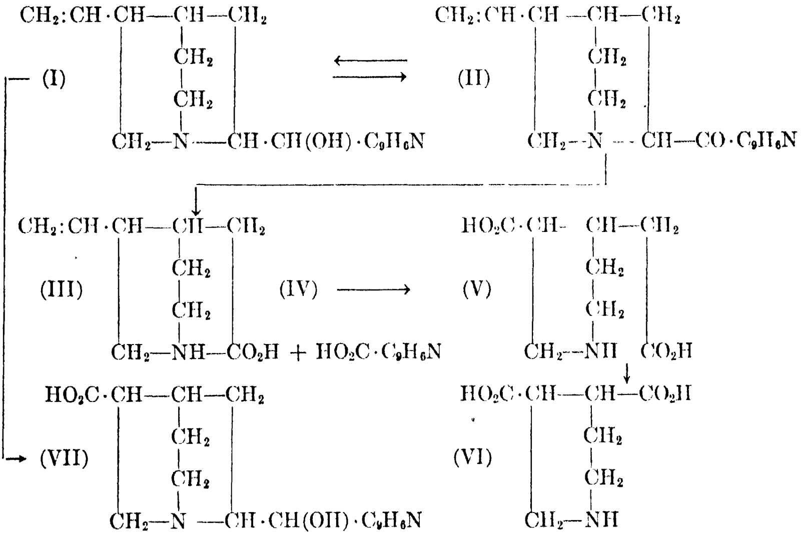


α-Isocinchonine

Quinine is methoxycinchonidine or *6′-methoxy-3-vinylruban-9-ol*, since the hypothetical parent compound of quinine has been given the name rubane (see formula and *Rabe*, Ber. **55**, 522). When quinine is heated with hydrochloric acid at 150°, the methyl group is split off, leaving *apoquinine*, m.p. 210° (dec.), $[\alpha]_D$ −178° (alcohol); in the reaction there is a simultaneous transposition of the molecule. Demethylated quinine, hydroxycinchonidine, $C_{19}H_{22}N_2O_2$, has been found in *China cuprea*, a bark derived from *Remija pedunculata*, and is termed *cupreine*, m.p. 198° (anhydrous), $[\alpha]_D^{17}$ −175° (alcohol). With methylating agents cupreine gives quinine (*the methyl ether of cupreine*), and with hydrochloric acid at 140°, apoquinine.

Catalytic reduction of the vinyl group of cupreine yields *hydrocupreine*, $C_{19}H_{24}N_2O_2$, which can also be obtained by demethylation of dihydroquinine (*Kelber*, Ber. **49**, 55; *Giemsa, Halberkann*, Ber. **51**, 1325).

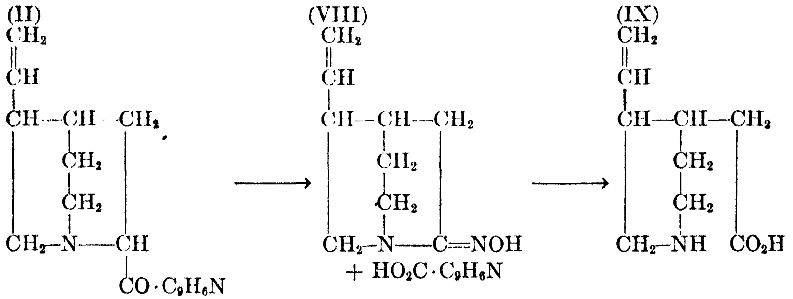
Oxidative Decomposition of the Cinchona Bases. (*Koenigs*, Ber. **35**, 1357; *Rabe*, Ber. **49**, 2753). Cinchonine (I) is converted by careful oxidation with chromic acid to the ketone corresponding to the secondary alcohol, *cinchoninone* (II), m.p. 126°, from which cinchonine can be regenerated by reduction. Quinine, on similar treatment, yields *quininone*, m.p. 108°. The ketones obtained from cinchonidine and quinidine are identical with cinchoninone and quininone. Strong oxidation with chromic acid decomposes cinchonine and quinine to *cinchoninic acid* (4-quinolinecarboxylic acid) (IV) (p. 241) or *quinic acid* (methoxyquinoline-4-carboxylic acid) and *meroquinene* (III), m.p. 224° (dec.) (μέρος, portion). The latter, on further oxidation with $KMnO_4$, gives *cincholoiponic acid* (λοιπός, remaining), 3-carboxy-4-piperidineacetic acid, m.p. 222° (anhydrous) (V), and then *loiponic acid*, hexahydrocinchomeronic acid (VI), m.p. 259°. With the calculated amount of dilute permanganate solution, cinchonine is oxidized, with simultaneous elimination of formic acid, to *cinchotenine* (VII), m.p. 197°, and quinine is similarly oxidized to quinotenine.



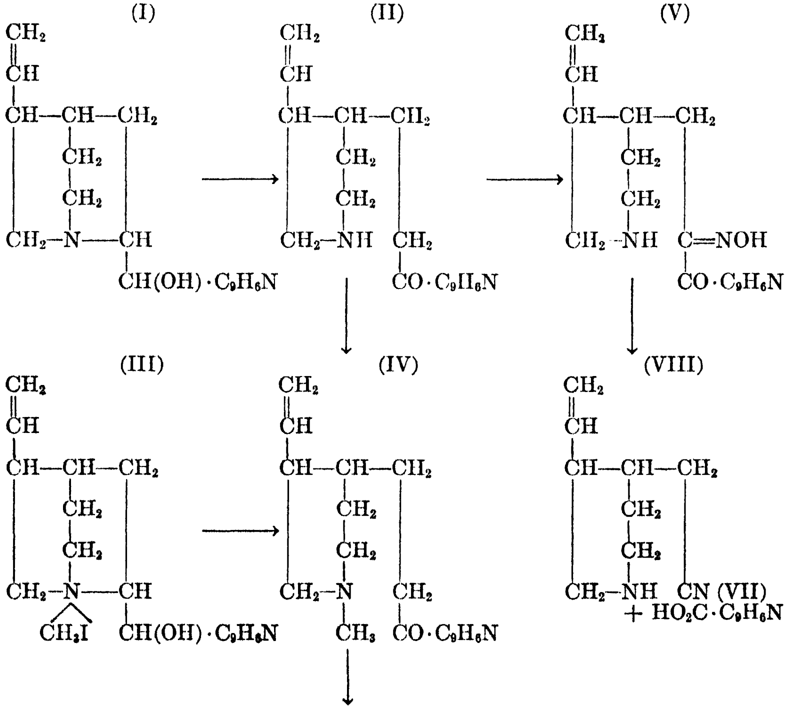
For the action of ozone on the cinchona alkaloids, see *Seekles*, Rec. **42**, 69.

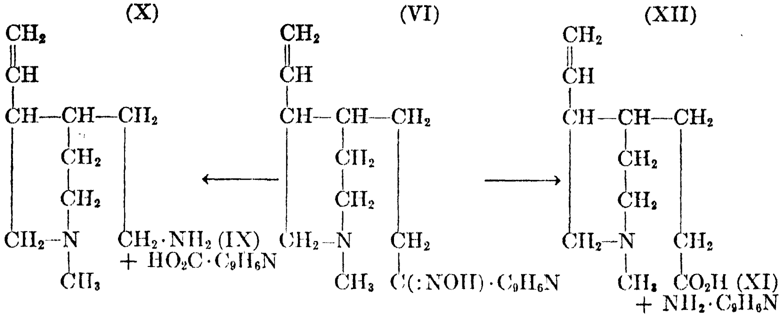
With hydrogen peroxide crystalline N-oxides are formed (*Speyer, Becker*, Ber. **55**, 1321).

The primary oxidation product of cinchonine, cinchoninone, m.p. 127°, is a tautomeric substance. In the keto form it forms an oxime, and in the enol form it reacts with acetyl and benzoyl chloride to give the corresponding acetyl and benzoyl derivatives. Cinchoninone is decomposed by the action of amyl nitrate and sodium ethylate to cinchoninic acid and *isonitrosovinylquinuclidine* (VIII), an inner amidoxime which yields hydroxylamine and *meroquinene* (IX) on saponification (*Rabe*, Ber. **41**, 62; Ann. **365**, 353). The fact that *quininone*, when subjected to the same series of reactions, gives the same isonitroso derivative is noteworthy from the stereochemical viewpoint (*Rabe*, Ann. **373**, 89).



Disintegration of the Cinchona Alkaloids: the Quinatoxines (*Rubatoxanones: Rabe*, Ber. **55**, 523).—The disintegration of the bicyclic or "second half" of the cinchona bases, already noted in their oxidation, occurs with remarkable facility in other reactions. When cinchonine (I below) or quinine is digested for a long time with dilute acetic acid, the bond between the nitrogen atom and the neighboring CH-group is broken, and the CH(OH)-group is converted to a keto-group. (*v. Miller, Rohde*, Ber. **33**, 3214). The velocity of this isomerization increases with decreasing dissociation constant of the acid used; it is therefore greater in organic acids than in mineral acids (*Rabe*, Ber. **43**, 3308; *Biddle*, Ber. **45**, 527). Cinchonine gives the isomeric *cinchotoxine* (II), m.p. 59°, which, like the corresponding quinotoxine (yellow oil, $[\alpha]_D$ +38.4°; hydrochloride m.p. 180°), is very poisonous and has no antipyretic action. The "toxines" from cinchonidine and quinidine are identical with those obtained from cinchonine and quinine. A similar decomposition occurs when the methyl iodide addition product of cinchonine (III) is boiled with alkali or dilute acetic acid, HI being eliminated and N-



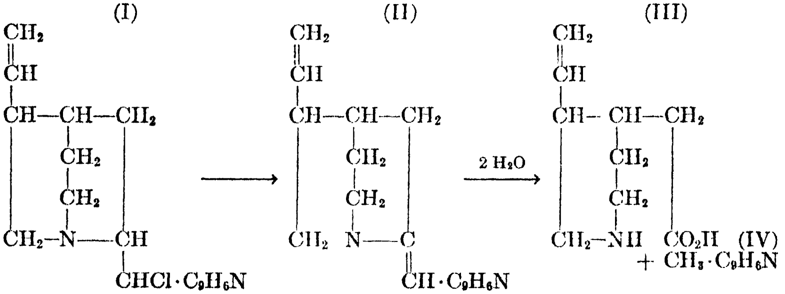


methylcinchotoxine (IV) formed; the latter can also be obtained by methylation of cinchotoxine. With nitrous acid cinchotoxine gives a monoisonitroso compound. The *Beckmann* rearrangement of this isonitrosocinchotoxine (V) and of N-methylcinchotoxine oxime (VI) gives interesting products. The former decomposes into cinchoninic acid (VII) and the nitrile of meroquinene (VIII). With N-methylcinchotoxine oxime the rearrangement takes two courses, one yielding cinchoninic acid (IX) and 1-methyl-3-vinyl-4-(aminoethyl)-piperidine (X), and the other leading to 4-aminoquinoline (XI) and N-methylhomomeroquinene (XII) (*Königs*, Ber. **40**, 648, 2873; *Rabe, Milarch*, Ann. **382**, 365).

Cinchotoxine has been used for a partial synthesis of cinchonine. With hypobromous acid it forms a bromoimine, which is converted by elimination of 1 HBr with sodium ethylate to cinchoninone; the latter can be reduced to cinchonine (*Rabe*, Ber. **44**, 2088; *Rabe, Kindler*, Ber. **51**, 466; see formulas, p. 356). The synthesis of quinuclidine, which is similar to the second part of the cinchona bases, has already been described (p. 224).

Decomposition of Cinchonine Chloride and Quinine Chloride (*Koenigs*, J. pr. **61**, 1).—When cinchonine and quinine are treated with PCl_5, *cinchonine chloride* (I), m.p. 72°, and *quinine chloride*, m.p. 151°, are formed. Digestion with alcoholic KOH converts these by elimination of HCl to *cinchene* (II) and *quinene*, which are also obtained from cinchonidine and quinidine by similar treatment. (For the constitution of these unsaturated derivatives, *cf. Rabe*, Ber. **55**, 524, footnote.) However, when the chlorides of these four alkaloids, cinchonine, cinchonidine, quinine, and quinidine chloride, are reduced, the chlorine atoms are replaced by hydrogen atoms, with formation of four different desoxy compounds: *desoxycinchonine, desoxycinchonidine, desoxyquinine*, and *desoxyquinidine*.

Cinchene and quinene decompose with simultaneous addition of water in two different ways. When heated with 20% aqueous phosphoric acid cinchene and quinene yield lepidine (IV) or methoxylepidine and meroquinene (III).

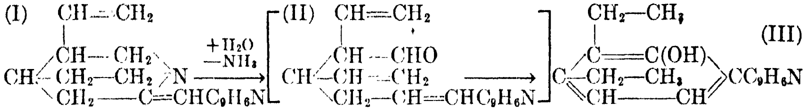


On prolonged boiling with hydrobromic acid, cinchene and quinene split ammonia and some methyl bromide and add water, forming *apocinchene* and *apoquinene:*

$$C_{19}H_{20}N_2 \text{ (cinchene)} + H_2O = C_{19}H_{19}NO \text{ (apocinchene)} + NH_3$$

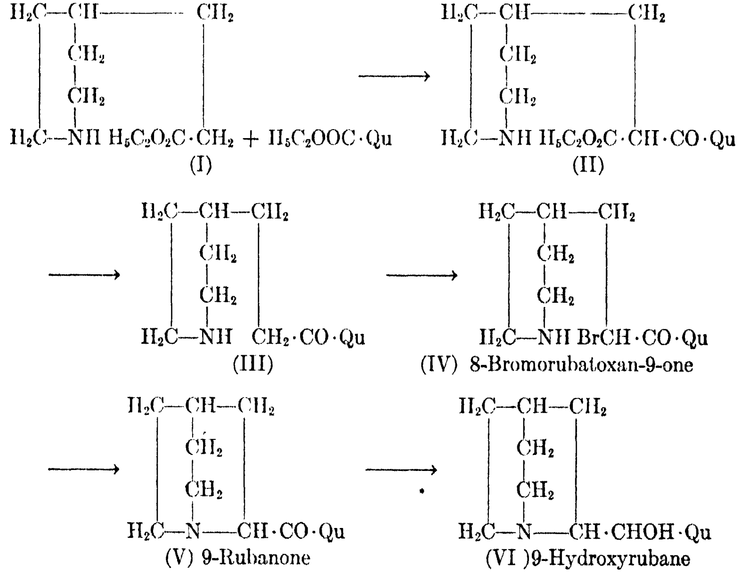
By decomposition and partial synthesis apocinchene has been identified as **4-(2-hydroxy-3,4-diethylphenyl)quinoline**; apoquinene is, therefore, **4-(2-hydroxy-3,4-diethylphenyl)quinolinol**.

The formation of apocinchene, 4-(2-hydroxy-3,4-diethylphenyl)quinoline (III) by hydrolysis of cinchene (I), is outlined in the following equations:



The rearrangement of the hypothetical intermediate product (II) into the phenylquinoline derivative is analogous to the conversion of olefinic terpenes to cyclic compounds, *e.g.*, the formation of isopulegol from citronellal.

Synthesis of Cinchona Alkaloids.—Since the conversion of cinchotoxine to cinchonine has already been described, only the formation of the second half of the cinchona alkaloids is necessary to complete a total synthesis. This may be considered fulfilled by the synthesis of *quinuclidine* (p. 224), 3-*ethylquinuclidine* (p. 224) and *cincholoiponic acid* (p. 225), on the one hand, and of cinchoninic acid or quininic acid, on the other. However, the fusion of the two sections is still lacking. Some promising work has been done on this problem (*Rabe, Kindler*, Ber. **51**, 1360; **52**, 1842; *Rabe, Kindler, Wagner*, Ber. **55**, 532). According to these investigations, the quinuclidine section can be introduced into the molecule as *homocincholoipone* (I); at the present time, however, no total synthesis for this compound is known (*Koenigs, Ottmann*, Ber. **54**, 1343). To form dihydrocinchonine the homocincholoipone is condensed with ethyl cinchoninate by an acetoacetic ester condensation to the 1,3-oxocarboxylic acid ester (II), which is easily converted to *rubatoxanone* (III). At this point the synthesis becomes analogous to the partial synthesis of cinchonine from cinchotoxine. In this simpler case it proceeds through IV to the vinyl-free 9-*rubanone* (V) and then by reduction to 9-*hydroxyrubane* (VI) (Qu = 4-quinolyl).



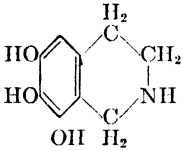
The exceptional curative action of quinine has instigated many attempts to prepare a more efficacious derivative. *Ethylhydrocupreine* is used medicinally as *optochine*, and the *isoamyl-* and *isoöctylhydrocupreines* as *eucupine* and *vuzine*.

VI. ALKALOIDS OF THE ISOQUINOLINE GROUP

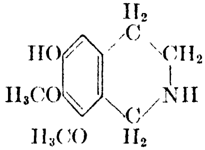
1. Several of the alkaloids of the anhalonium base type have been identified, principally through the investigations of *Späth*, as simple derivatives of isoquinoline. They are obtained from the flower substances of *Anhalonium Lewinii*, *A. Williamsi* or *A. fissuratum*.

Anhalamine, $C_{11}H_{15}O_3N$, m.p. 185.5°; **anhalonidine**, $C_{12}H_{17}O_3N$, m.p. 154°; **anhalonine**, $C_{12}H_{15}O_3N$, m.p. 85°; **pellotine**, $C_{13}H_{19}O_3N$, m.p. 110°; **lophophorine**, $C_{13}H_{17}O_3N$, sirup.

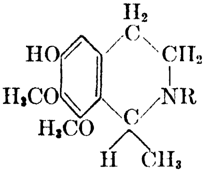
All these bases are derivatives of 1,2,3,4-*tetrahydroisoquinoline*-6,7,8-*triol* (I)



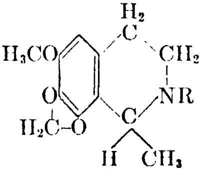
(I)



Anhalamine

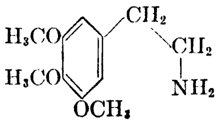


R = H, Anhalonidine
R = CH_3, Pellotine



R = H, Anhalonine
R = CH_3, Lophophorine

The determination of the constitution of these bases was accomplished with the aid of a similar base, **mezcaline**, $C_{11}H_{17}O_3N$, b.p. 180° (12 mm.), which had already been proved by synthesis to be trimethoxyphenethylamine (*Späth*, Ber. **40** 129; **42**, 263). The relationship between this substance and the anhalonium bases is evident from its formula:



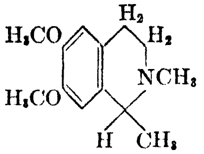
Mezcaline

and also from its condensation with formaldehyde to the bicyclic anhalonium bases (*Späth*, Mo. **42**, 97).

The position of the free hydroxy group has been established by synthesis for all the alkaloids.

Syntheses: anhalamine (*Späth*, *Röder*, Mo. **43**, 93); anhalonidine and pellotine (*Späth*, Mo. **42**, 97); anhalonine and lophophorine (*Späth*, *Gangl*, Mo. **44**, 103).

Another simple isoquinoline derivative is the alkaloid **carnegine**, $C_{13}H_{19}O_2N$, hydrochloride, m.p. 228°, optically inactive; it has been isolated from *Carnegiea gigantea* [*Heyl*, Arch.Pharm. **266** (1929), 668]. Its formula has been proved by synthesis (*Späth*, Ber. **62**, 1021).



Carnegine

2. OPIUM BASES. Opium, the dried juice of the green seed capsules of poppy (*Papaver somniferum*), contains, besides meconic acid (3-hydroxy-1,4-pyrone-2,6-dicarboxylic acid) and meconine (5,6-dimethoxyphthalide), a series of bases of which the most important are:

Morphine, $C_{17}H_{19}NO_3$ (to 12%)
Codeine, $C_{18}H_{21}NO_3$ (0.3%)
Thebaine, $C_{19}H_{21}NO_3$ (0.4%)
Neopine, $C_{18}H_{21}NO_3$
Papaverine, $C_{20}H_{21}NO_4$ (0.8%)

Narcotine, $C_{22}H_{23}NO_7$ (to 8%)
Narceine, $C_{23}H_{27}NO_8$ (0.2%)
Laudanosine, $C_{21}H_{27}NO_4$ (0.0008%)
Laudanine } $C_{20}H_{25}NO_4$
Laudanidine }

From the determination of the molecular composition of morphine in 1848 to the postulation of the currently accepted structure for morphine (1923), 75 years elapsed; during this time many able chemists investigated the problem, and contributed a body of data which laid the foundation for the later clarification of the morphine structure. The simplest of this group of alkaloids (papaverine and the like) were early recognized as derivatives of isoquinoline, and morphine, codeine, and thebaine are now known to contain isoquinoline rings also (see p. 249). For the development of these investigations, consult the following references: *P. Kappelmeier*, Die Konstitutionserforschung der wichtigsten Opiumalkaloide, Stuttgart, 1912 (Ahrens-Sammlung); *Gulland, Robinson*, J. **123**, 980 (1923), and the literature references listed there; *Schöpf*, Die Konstitution der Morphiumalkaloide, Ann. **452**, 211.

MORPHINE, $C_{17}H_{17}NO(OH)_2 + H_2O$, m.p. 254° (dec., anhydrous), $[\alpha]_D$ −130.9° (methanol), crystallizes from alcohol in small prisms, has a bitter taste and in small quantities produces sleep. It is a tertiary monoacid base, having an alkaline reaction. Its officinal hydrochloride, $C_{17}H_{19}NO_3 \cdot HCl + 3\,H_2O$, $[\alpha]_D$ −100.7° (H_2O), *morphinum hydrochloricum*, forms delicate silky needles; it is widely used as a means of producing pain-killing sleep.

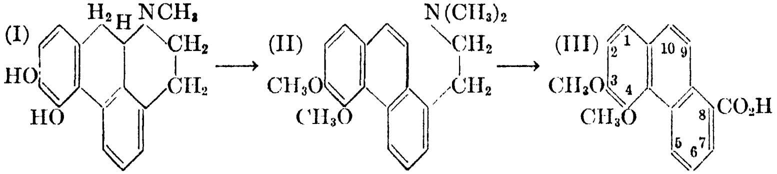
Morphine was the first alkaloid to be isolated from a plant (*Sertürner*, 1806). Its composition was determined by *Laurent* in 1848.

The solutions of morphine and its salts are colored dark blue by ferric chloride. The solutions in concentrated sulfuric acid turn blue-red on addition of a little nitric acid. Morphine is readily oxidized by $KMnO_4$ in the presence of bicarbonate, 2 molecules joining, with loss of two hydrogen atoms, to form **pseudomorphine,** $(C_{17}H_{18}NO_3)_2$ [*Vongerichten*, Ann. **294**, 206; *Balls*, J.Biol.Chem. **71** (1929), 537], which has also been isolated from opium. When reduced with hydrogen and colloidal platinum, morphine adds two atoms of hydrogen, yielding dihydromorphine, $C_{17}H_{21}O_3N$ (*Knorr, Hess*, Ber. **44**, 2865). Morphine contains two hydroxyl groups, and behaves as a phenol alcohol, forming salts with only one atom of metal, but giving two acetyl derivatives. Diacetylmorphine is used officinally under the name *heroine*. The third oxygen atom of the morphine molecule is inactive. On distillation with zinc dust morphine yields phenanthrene (see p. 361, structural formula) and a mixture of two bases (*Vongerichten*, Ber. **34**, 1162).

For the effect of ozone on morphine and hydrogenated bases of the morphine series, see *Speyer, Popp*, Ber. **59**, 390; *Speyer, Roell*, Ber. **63**, 539.

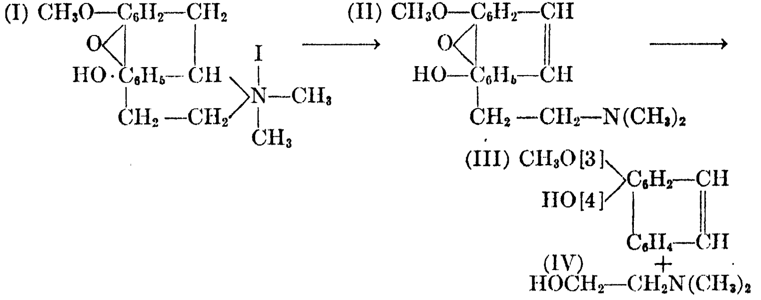
On treatment with phosphorus halides or anhydrous liquid hydrogen halide acids, the alcoholic hydroxyl group in morphine is replaced by halogen. The chloromorphide, $C_{17}H_{17}ClN(OH)O$, and bromomorphide so formed yield three bases isomeric with morphine, α-, β- and γ-isomorphine, on hydrolysis (*cf.* the analogous reaction with codeine) (*Oppé*, Ber. **41**, 975).

Apomorphine, 10,11 - *dihydroxy* - 6 - *methyl* - 5,6,6a,7 - *tetrahydro* - 4 - *dibenzo[de, g]quinoline,* $C_{17}H_{17}NO_2$ (I) is obtained from morphine by the elimination of one molecule of water by the action of concentrated hydrochloric acid at 140–150° or of other dehydrating agents, such as sulfuric acid, phosphoric acid, or oxalic acid. It differs markedly from morphine in its physiological properties; it is not a narcotic, but a strong emetic. Its methyl bromide addition product is used medicinally under the name *Euporphine.* Apomorphine, unlike morphine, contains two phenolic hydroxyl groups. Its dimethyl ether can be converted by exhaustive methylation first to *dimethylapomorphimethine,* 8-β-dimethylaminoethyl-3,4-dimethoxyphenanthrene (II), then to 3,4-*dimethoxy*-8-*vinylphenanthrene,* which can be oxidized to 3,4-*dimethoxyphenanthrene*-8-*carboxylic acid* (III) (*Pschorr,* Ber. **40,** 1984). Since the place of attachment of the nitrogen atom is known from the relationship between morphine and codeine (see under hydroxycodeine), the structure of apomorphine may be considered established. (For the synthesis of the dimethyl ether of apomorphine, see p. 370.)

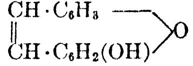


From a comparison with the similar transformation of thebaine to morphothebaine (p. 362) it is evident that the transition from morphine to apomorphine must be attended by such an extensive rearrangement that the structure of morphine cannot be proved from that of apomorphine. For the individual phases of the formation of apomorphine, see *Schöpf, Borkowsky,* Ann. **458,** 162.

Codeine, $C_{17}H_{17}NO(OCH_3)OH$, hydrate, m.p. 155°, $[\alpha]_D$ −137.7° (alcohol), sulfate, m.p. 278° (dec.), is present in opium and can be prepared by methylating morphine with KOH and methyl iodide or dimethyl sulfate or diazomethane, or technically by methylating the sodium salt of morphine with trimethylphenylammonium chloride (Ger. Pat. 247180, 1909; Frdl. **X,** 1215); therefore it must be methylmorphine (*Grimaux,* C.r. **92,** 1140; Ger. Pat. 102634, 1898). Its methyl iodide addition product (I) is converted by heating with alkali to α-methylmorphimethine (II), m.p. 118°. This is decomposed by warm acetic anhydride to the acetic acid ester of β-hydroxyethyldimethylamine (IV) and methylmorphol, 4-hydroxy-3-methoxyphenanthrene (III) (*Knorr,* Ber. **37,** 3494):

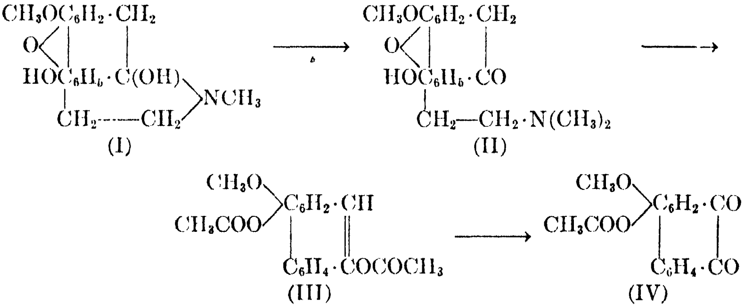


The identification of morphol as 3,4-dihydroxyphenanthrene (synthesis: Vol. III, p. 674) follows from its oxidation to morpholquinone (3,4-dihydroxyphenanthrenequinone) and then to phthalic acid, and also from the formation of dimethylmorphol (3,4-dimethoxyphenanthrene) from 2-amino-3,4-dimethoxy-α-phenylcinnamic acid (*Pschorr, Sumuleanu,* Ber. **33,** 1810; *Vongerichten,* Ber. **33,**

1824). The fission of the methyl iodide addition product of α-methylmorphimethine by alcoholic alkali yields trimethylamine and morphenol, 3-hydroxyphenanthro[4,5-*bcd*]furan 
$\left.\begin{matrix}CH\cdot C_6H_3\\ \| \\ CH\cdot C_6H_2(OH)\end{matrix}\right\rangle O$ (*Vongerichten*, Ber. **33**, 352; **34**, 2722).

The elimination of the nitrogen as an ester of β-hydroxyethyldimethylamine proves the presence of the group $H_3CN\cdot C\cdot C$ in the alkaloid.

By careful oxidation with chromic acid codeine is converted to a **hydroxycodeine,** $C_{17}H_{16}NO(OCH_3)(OH)_2$ (I). This compound contains two alcoholic hydroxyl groups, and, like codeine, yields by decomposition of its methyl iodide addition product hydroxymethylmorphimethine (II). When heated with acetic anhydride the latter decomposes into β-dimethylaminoethyl acetate and 3 methoxy-4,9-diacetoxyphenanthrene (III), which oxidizes to a ketone, methy acetylmorpholquinone, 3-methoxy-4-acetoxyphenanthrenequinone (IV).



Hence it follows: (*a*) that the hydroxyl group acquired in the first step of this decomposition is attached to one of the linking carbon atoms of the phenanthrene nucleus (9 or 10); (*b*) that the phenanthrene bridge in morphine alkaloids is hydrogenated, since this hydroxyl group is alcoholic in nature; and (*c*) from the conversion of the hydroxyl group to a carbonyl group in the transformation of hydroxycodeine to hydroxymethylmorphimethide, that "*in the morphine alkaloids the nitrogen of the side-ring is attached to the hydrogenated bridge of the phenanthrene nucleus*" (*Pschorr, Einbeck*, Ber. **40**, 1980; *Knorr, Hörlein*, Ber. **40**, 2042).

Codeine is oxidized by permanganate in acetone solution or by hot chromic acid mixture to **codeinone,** $C_{18}H_{19}NO_3$, m.p. 186°, $[\alpha]_D$ $-205°$ (alcohol), whose oxime-forming ketone group is produced from the alcoholic hydroxyl group of morphine (see above). In contrast to codeine and in analogy with thebaine, codeinone is decomposed by boiling with acetic anhydride to the acetic acid ester of N-*acetyl*-N-*β-hydroxyethylmethylamine* and 3-*methoxy*-4,6-*dihydroxyphenanthrene*.

Dihydrocodeinone is used as a pharmaceutical under the name *dicodide*, the acetyl compound derived from its enol form under the name *acedicone*, and *dihydrohydroxycodeinone* under the name *eucodal*.

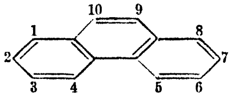
For the action of ozone on dihydrocodeine, see *Speyer, Popp*, Ber. **59**, 390; *Speyer*, Ber. **62**, 209; *Speyer, Roell*, Ber. **63**, 539.

For the conversion of codeine to thebenine and morphothebaine, see p. 362.

Like morphine, codeine also reacts with phosphorus halides, forming *chlorocodide*, $C_{17}H_{17}NCl(OCH_3)O$, and *bromocodide* by replacement of the alcoholic hydroxyl group by halogen. These products do not regenerate codeine on hydrolysis, but form, according to the conditions, three isomers of codeine, *isocodeine, pseudocodeine*, and *allopseudocodeine*, which can also be obtained by methylation of the corresponding isomorphines (*Speyer, Wieters*, Ber. **54**, 2647; *Speyer, Krauss*, Ann. **432**, 233). The isocodeine is a stereoisomer of codeine, since oxidation with CrO_3 converts them to the same codeinone (see above). Pseudocodeine and allopseudocodeine are structurally identical, and yield on oxidation a *pseudocodeinone*, isomeric with codeinone; the methyl iodide addition product of this oxidation product decomposes when boiled with alcohol to 3-methoxy-4,8-dihydroxyphenanthrene. The conversion of codeine to pseudocodeine and allopseudocodeine is therefore accompanied by a shifting of the alcoholic hydroxyl group from position 6 to position 8 of the phenanthrene nucleus. Since the replacement of the OH-group by hydrogen results in the production of the same *desoxycodeine* $C_{18}H_{21}NO_2$ from all the isomeric forms of codeine, these isomers must all have the same C—N skeleton, and therefore position 8 is eliminated as the site of attachment of the side-ring. Also, position 7 of the phenanthrene nucleus is excluded from consideration because codeinone and pseudocodeinone contain a reactive CH_2-group next to the carbonyl group.

If we summarize the data concerning the structure of morphine and codeine, we obtain the following picture:

1. Presence of a phenanthrene nucleus:



2. In the 3-position of the phenanthrene nucleus morphine is substituted by a hydroxy group, and codeine by a methoxy group; the ether-like oxygen atom is in the 4-position and the alcoholic hydroxyl group is in the 6-position in both alkaloids (from the constitution of methylmorphol).

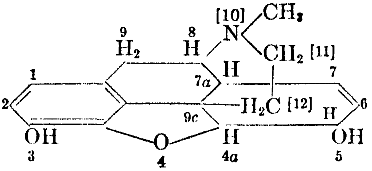
3. An easily hydrogenated double bond, in the α,β-position to the alcoholic hydroxyl group (dihydro products, conversion of codeine to pseudocodeine).

4. A radical, $H_3CN \cdot CH_2 \cdot CH_2$—, from the fission of $(H_3C)_2N \cdot CH_2CH_2OH$ from morphol.

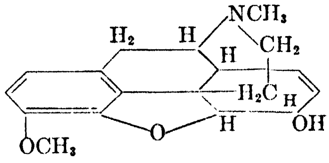
5. The nitrogen member is attached to the 9- or 10-position of the phenanthrene nucleus (see hydroxycodeine).

6. The other end of the nitrogen-containing group cannot be joined in the 8-position (from the conversion of codeine to pseudocodeine), in the 7-position (since codeinone, dihydrocodeinone and pseudocodeinone each contain a reactive methylene group) nor in the 6-position of the phenanthrene nucleus (since this is the site of the secondary alcoholic group).

The second point of attachment of this side-ring must therefore be the C-atom in the 5-, 4*b*-, or 8*a*-position of the phenanthrene nucleus, which corresponds to the 4*a*-, 9*c*-, or 7*a*-position in the morphine molecule (see formula below), respectively. This most difficult problem in the determination of the structure of morphine was solved by the discovery through clever experimental work (see below) that only the 9*c*-(4*b*- in the phenanthrene formula) position is available for this linkage. Thus the complete formula for morphine and codeine was first presented by *Gulland* and *Robinson* (J. **123,** 980) and later completely confirmed by *Schöpf* (Ann. **452,** 211):



Morphine



Codeine

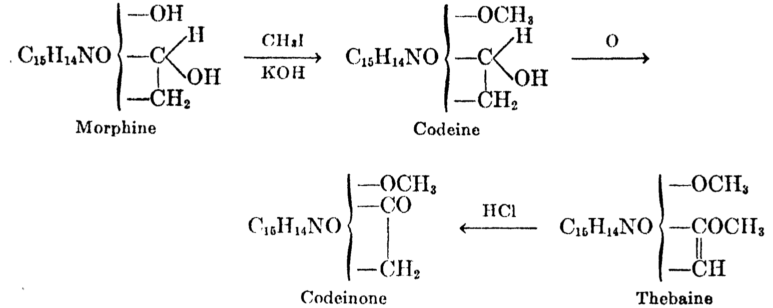
According to these formulas, the principal alkaloids of the opium group are derivatives of hydrogenated isoquinoline; the nitrogen atom and the C-atoms 11, 12, 9*c*, 7*a*, and 8 form the heterocyclic ring.

For variations of the codeine molecule, and their effect on the physiological properties, see *v. Braun*, Ber. **59,** 1081.

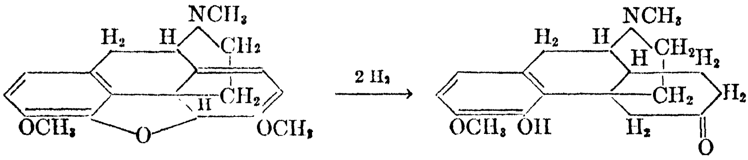
Neopine (*β-codeine*), $C_{18}H_{21}O_3N$, m.p. 127.5°, has been isolated from the last residual liquor of the opium alkaloids. It is a structural isomer of codeine (double bond from 7-C to 7*a*-C; *v. Duin, Robinson, Smith,* J. **1926,** 903).

Thebaine, $C_{17}H_{15}NO(OCH_3)_2$, silvery plates, m.p. 193° $[\alpha]_D$ −218° (alcohol), is converted to codeinone by elimination of a methyl group with dilute mineral acids. Thebaine is therefore the methyl ether of the enol form of codeinone.

The relationships among the three opium alkaloids—morphine, codeine, and thebaine—are summarized by the following (*Knorr*, Ber. **39**, 1409):



On catalytic hydrogenation thebaine yields a mixture of hydrogenated products, from which *dihydrothebainone*, *dihydrothebaine* (m.p. 162°; picrate m.p. 238°) and *tetrahydrothebaine* (m.p. 83°; hydrochloride m.p. 116°) can be isolated (*Schöpf*, Ann. **452**, 240). The formation of a tetrahydrothebaine indicates that thebaine contains two double bonds. This result, and the relationship between codeinone and thebaine, gives formula (I) for thebaine.



(I) (II)

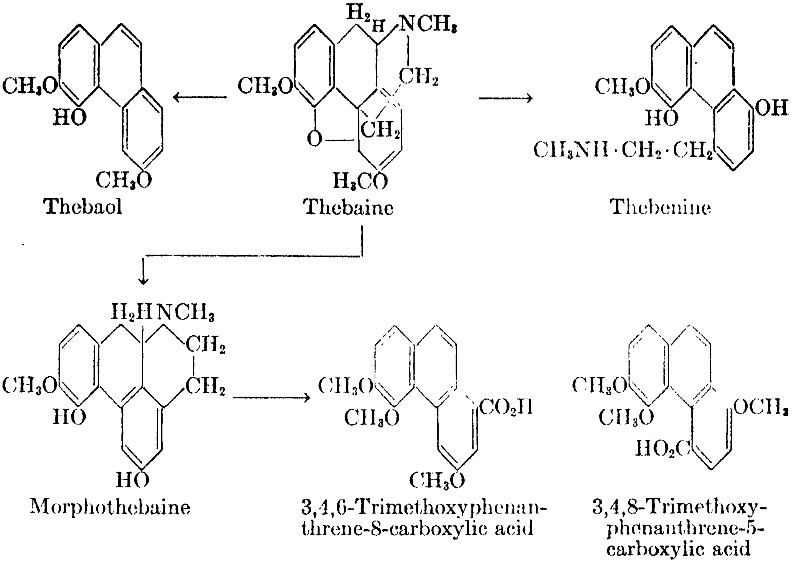
On catalytic hydrogenation of thebaine (palladium black + H_2) the oxide ring opens very readily. Further investigation has shown that this reductive fission under mild conditions, leading to the formation of a phenolic hydroxyl group, is a characteristic of those derivatives of morphine which contain a double bond from the 5-C to the 6-C. Therefore the catalytic hydrogenation of thebaine also yields, with simultaneous saponification of the methoxy group, *dihydrothebainone* (II), m.p. 140° (oxime, m.p. 240–245°) (*Schöpf*, Ann. **452**, 235).

The oxide ring can also be very easily formed; the dihydrothebainone can be converted to *dihydrocodeinone*. For several such partial syntheses in the morphine series, see *Schöpf*, *Pfeifer*, Ann. **483**, 157; for the method used in this case, see the section on sinomenine.

Reactions and Decomposition of Thebaine.—When boiled with acetic anhydride, thebaine is split into *β-(methylamino)-ethyl acetate* and the acetyl ester of 3,6-*dimethoxy*-4-*hydroxyphenanthrene*, *thebaol*; the latter has been synthesized from 2-amino-3,4-dimethoxy-α-(*p*-methoxyphenyl)-cinnamic acid (*Pschorr*, *Seydel*, *Stöhrer*, Ber. **35**, 4400).

Thebaine reacts with warm hydrochloric acid in either of two ways, depending on the concentration of the acid. By short warming with dilute hydrochloric acid a secondary base, *thebenine*, $C_{17}H_{14}N(OH)_2(OCH_3)$, is formed; concentrated hydrochloric acid produces an isomeric tertiary base, *morphothebaine*, $C_{17}H_{14}N(OH)_2(OCH_3)$, with intermediate formation of a halochromic red compound (*Schöpf*, *Borkowsky*, Ann. **458**, 148). Under the same conditions codeinone (p. 360) also forms thebenine and morphothebaine. Morphothebaine is an analogue of apomorphine (p. 359). Its dimethyl ether is decomposed by exhaustive methylation to 3,4,6-trimethoxy-8-vinylphenanthrene, which can be oxidized to

3,4,6-trimethoxyphenanthrene-8-carboxylic acid (*Pschorr*, Ann. **373,** 52; *Pschorr, Knöffler*, Ann. **382,** 50). During the conversion of thebaine to morphothebaine the side-ring shifts from the 9*c*-C to the 7-C, after temporarily resting on the 7*a*-C (a retropinacoline rearrangement) (*meta*-thebainone series: *Schöpf, Perrey*, Ann. **483,** 169). For details of the reaction mechanism of the formation of morphothebaine, see *Schöpf, Borkowsky*, Ann. **458,** 160.

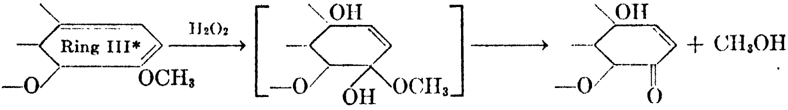


Thebaol Thebaine Thebenine

Morphothebaine 3,4,6-Trimethoxyphenanthrene-8-carboxylic acid 3,4,8-Trimethoxyphenanthrene-5-carboxylic acid

Thebenine is converted by an analogous series of reactions (exhaustive methylation, oxidation of the des-base) to 3,4,8-trimethoxyphenanthrene-5-carboxylic acid. In the formation of thebenine, the OH-group wanders from position 5 to position 7, and the heterocyclic side-ring shifts from 9*c*-C to the 4*a*-C. A similar wandering of the hydroxyl group occurs in the transition of codeine to pseudocodeine (p. 360). This condition is verified by the formation of triacetylthebaine by heating pseudocodeinone with acetic anhydride (*Pschorr*, Ann. **373,** 56). For the individual phases of the formation of thebenine, see *Schopf, Borkowsky*, Ann. **458,** 162.

Thebaine is converted by hydrogen peroxide to *hydroxycodeinone* (*Freund, Speyer*, J. pr. **94,** 135; *Schöpf*, Ann. **452,** 249). This hydroxyketone, formed by a 1,4- addition of H_2O_2 to thebaine, contains a hydroxy group on the 7*a*-C:



Hydroxycodeinone

For the products of the reaction of thebaine with ozone, thebaizone, see *Wieland, Small*, Ann. **467,** 17.

Another alkaloid with a structure like morphine, *sinomenine*, is not found in opium, but in a climbing plant native to southern Japan, *Sinomenium acutum.* It is used as a remedy for rheumatism.

Sinomenine, $C_{19}H_{23}NO_4$, m.p. 182° (161°), $[\alpha]_D$ −70.7°; hydrochloride m.p. 231°. The proof of its constitution is due to the work of the Japanese investigators *Kondo, Ochiai* (Ann. **470,** 224) and *K. Goto* [*Goto, Sudzuki*, Bull. Chem. Soc. Japan **4** (1929), 163, 224].

According to the results of their work, *sinomenine* (analyzed by the *Zeisel* method) contains two CH_3O— and one CH_3N— group, and, since it dissolves in aqueous sodium hydroxide, a phenolic hydroxyl group. Of the four oxygen atoms, three are thereby taken into account; the fourth is in a ketone group, as is evident from the formation of an oxime, a semicarbazone, etc. An ethylene group in the molecule is easily saturated, with formation of *dihydrosinomenine*, $C_{19}H_{25}NO_4$, m.p. 199°.

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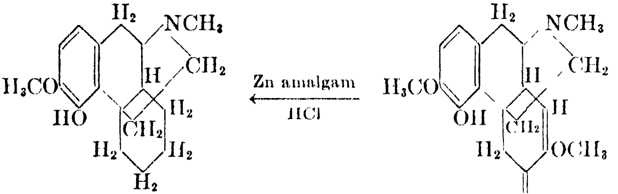
* The heterocyclic side-ring is omitted from the diagram.

As in the case of morphine, the *phenanthrene* nucleus was discovered by its formation in the zinc dust distillation of sinomenine. From this result alone, however, the alkaloid might also be an apomorphine derivative (see p. 359). The similarity of its reaction products to those of thebaine is shown by the following experimental data: When sinomenine is reduced by the *Clemmensen* method with zinc amalgam and hydrochloric acid, both methoxy groups and the keto group are removed and the double bond is hydrogenated. The *desoxytetrahydrosinomenine* so obtained was found to be the optical antipode of *dihydrothebacodine*, one of the electrolytic reduction products of *dihydrothebainone*; the constitution of dihydrothebacodine was already known (see below, and *Kondo, Ochiai*, Ber. **63**, 646). The constitution of *desoxytetrahydrosinomenine* is thereby established (*cf.* thebaine formula, p. 363):

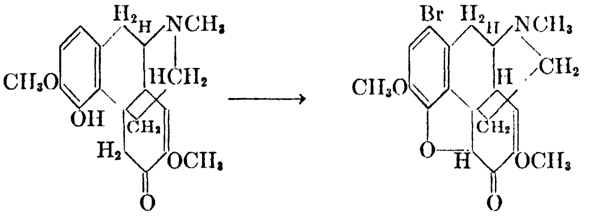


Desoxytetrahydrosinomenine = Dihydrothebacodine

Sinomenine

From the constitution of desoxytetrahydrosinomenine that of sinomenine can be derived, except for the positions of the methoxy and hydroxy groups eliminated in the reduction. To find these, sinomenine was fused with alkali, which converted it by loss of the nitrogen atom and the carbon atoms directly attached to it to *sinomenol*, $C_{16}H_{14}O_4$, m.p. 176°, a dihydric phenol. The dimethyl ether of this phenol is identical with the 3,4,6,7-*tetramethoxyphenanthrene* synthesized according to the *Pschorr* method. The free hydroxyl group and the 3-methoxy group must therefore occupy positions 4 and 7 of the phenanthrene nucleus, respectively (see the formula of sinomenine).

As its formula shows, sinomenine has the same ring skeleton as morphine, except that the oxide ring present in the opium alkaloids is missing, and its place is taken by a phenolic hydroxyl group on one side. Several alkaloids of the sinomenine series have been converted to derivatives of the codeine series by closure of the oxide ring. The formation of 1-bromo-7-methoxycodeinone from sinomenine is accomplished by treating the dibromo substitution product of the latter with alkali (*Schöpf*, Ann. **483**, 160):



Sinomenine

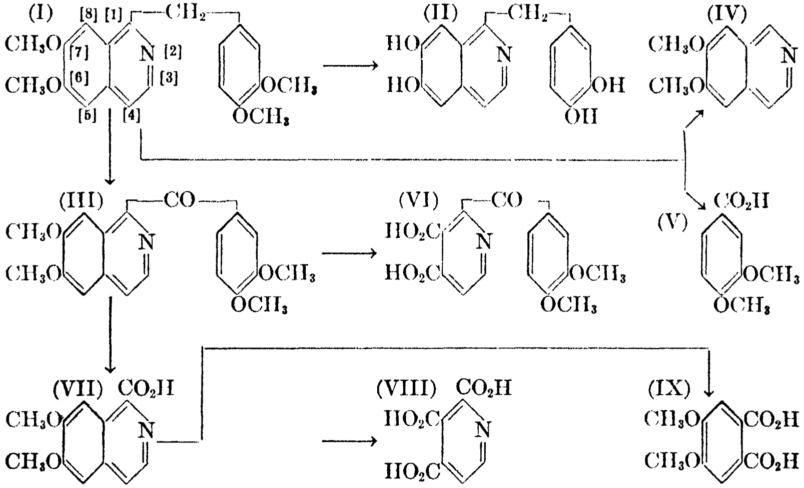
1-Bromo-6-methoxycodeinone

Similar conversions of dihydrothebanone to dihydrocodeinone and of dihydrohydroxythebainone to dihydrohydroxycodeinone have also been successful (*Schöpf, Pfeifer*, Ann. **483**, 158).

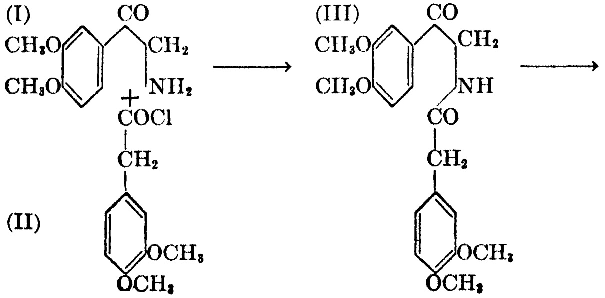
A number of alkaloids associated with morphine are derivatives of 1-*benzyl*-

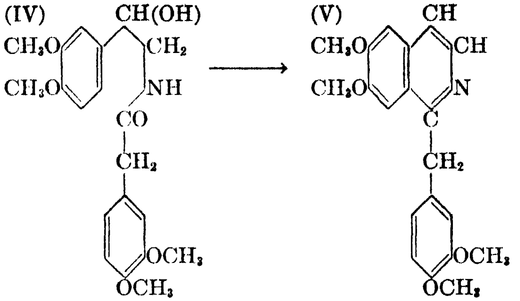
isoquinoline. Their structure was determined without difficulty, and has been verified by synthesis.

PAPAVERINE (I), 1-(3,4-*dimethoxybenzyl*)-6,7-*dimethoxyisoquinoline*, $C_{20}H_{21}NO_4$, m.p. 148°, optically inactive. Its constitution is evident from its decomposition products: Hydriodic acid splits off 4 CH_3I, leaving papaveroline (II). Potassium permanganate converts papaverine to papaveraldine, 1-(3,4-dimethoxybenzoyl)-6,7-dimethoxyisoquinoline (III), which is also found in opium (*Dobson, Perkin*, J. **99**, 135). Alkali fusion splits papaverine into 6,7-dimethoxyisoquinoline (IV) and veratric acid (V) (Vol. III, p. 366). Oxidation of papaveraldine yields papaveric acid, 2-(3,4-dimethoxybenzoyl)-pyridine-3,4-dicarboxylic acid (VI), 6,7-*dimethoxyisoquinoline*-1-*carboxylic acid* (VII), 2,3,4-*pyridinetricarboxylic acid* (VIII) and *metahemipinic acid* (IX) (*Goldschmiedt*, Mo. **9**, 327):



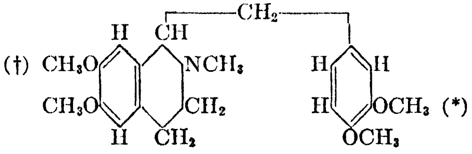
Synthesis of Papaverine (*Pictet*, Ber. **42**, 2943).—The isonitroso compound obtained from acetoveratrone (Vol. III, p. 352) with amyl nitrite and sodium ethylate is reduced by stannous chloride and hydrochloric acid to glycylveratrone (I). This condenses with homoveratric acid chloride (II) in the presence of alkali to N-homoveratroylglycylveratrone (III), which is reduced by sodium amalgam to β-veratroylamino-α-(3,4-dimethoxyphenyl)-ethanol (IV). The latter is converted by P_2O_5 in boiling xylene (*cf.* the isoquinoline syntheses, p. 250) to papaverine (V), $2\,H_2O$ being eliminated:





For other syntheses of papaverine from the readily obtainable 3,4-dihydropapaverine by dehydrogenation over Pd-asbestos, see *Späth, Burger,* Ber. **60**, 704, and *Mannich, Walther,* Arch.Pharm. **265** (1927), 1. For the synthesis of bases similar to papaverine, see *Mannich, Falber,* Arch.Pharm. **267** (1930), 601.

Laudanosine, $C_{21}H_{27}NO_4$, m.p. 89°, $[\alpha]_D$ +103.2°; the racemic form, m.p. 115°, occurs in very small quantities (about 0.0008%) in opium. It is closely related to papaverine, the hydrochloride of *dl*-laudanosine being obtained by reduction of the methyl chloride addition product of papaverine with tin and hydrochloric acid; it is therefore N-*methyltetrahydropapaverine*. *dl*-Laudanosine can be resolved by means of its quinate into optically active antipodes, the dextrorotatory modification being identical with the laudanosine found in opium. The synthesis of papaverine therefore includes that of laudanosine. For another synthesis, over dihydropapaverine, see *Pictet, Finkelstein,* Ber. **42**, 1979.

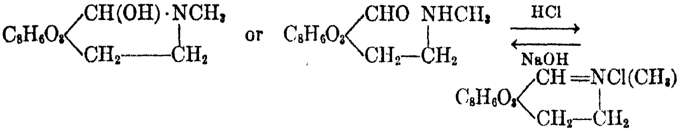


Laudanosine

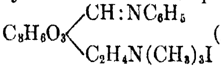
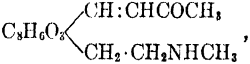
Laudanine, $C_{20}H_{25}NO_4$, m.p. 166° (optically inactive), and its levorotatory form, **laudanidine,** m.p. 177°, $[\alpha]_D$ −87.8° (chloroform), are similar in structure to laudanosine. They are the phenol bases corresponding to laudanosine, having an OH-group at the position marked (*) in the above formula. Laudanosine is converted to laudanine by heating with concentrated hydrochloric acid in a tube (*Späth, Burger,* Mo. **47**, 733). **Codamine,** m.p. 126°, occurring in opium, has the same structure as laudanosine except for an OH-group in place of the methoxy group at (†).

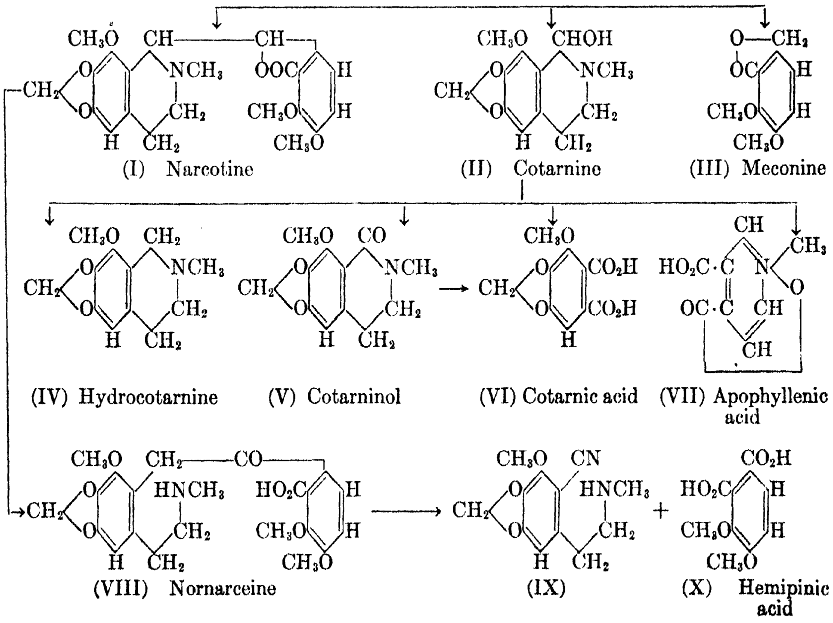
Narcotine (I) (see equations on p. 367), $C_{22}H_{23}NO_2$, m.p. 176°, $[\alpha]_D$ −198° (chloroform), is separated from morphine with aqueous potassium hydroxide, in which it is insoluble (*Robiquet,* 1817). When heated with alcohol or acetic acid at high temperatures, it racemizes to **gnoscopine** = *dl*-narcotine, m.p. 233°, which also occurs in opium, but probably as a product of narcotine. Gnoscopine can be resolved by means of its *d*-camphorsulfonate to *d*- and *l*-narcotine (*Perkin, Robinson,* J. **99**, 775). When heated with water at 140° narcotine is decomposed to *cotarnine* (II), $C_{12}H_{15}NO_4$, m.p. 125° [*Wöhler,* Ann. **50** (1844), 1], and meconine (III); the latter can be oxidized to opianic acid (3,4-dimethoxyphthalaldehydic acid) and hemipinic acid (3,4-dimethoxyphthalic acid).

Cotarnine is a "pseudo-ammonium base" of the isoquinoline series (*cf.* pp. 201, 230, and 251), from which salts of the true isomeric ammonium base are obtained with acids. These *pseudo*-bases, and also cotarnine, must exist in the desmotropic form as secondary amino alcohols [*Decker,* Ber. **33**, 2273; *Dobbi, Tinkler,* Proc.Chem.Soc. **20** (1904), 162]:



$$C_8H_6O_3\left\langle\begin{array}{l}CH(OH)\cdot NCH_3\\ CH_2\text{———}CH_2\end{array}\right. \text{ or } C_8H_6O_3\left\langle\begin{array}{l}CHO\ \ NHCH_3\\ CH_2\text{—}CH_2\end{array}\right. \underset{NaOH}{\overset{HCl}{\rightleftarrows}} C_8H_6O_3\left\langle\begin{array}{l}CH{=}NCl(CH_3)\\ CH_2\text{—}CH_2\end{array}\right.$$

This desmotropic character of cotarnine explains some of its contradictory reactions. Cotarnine, in the aldehydic form, yields an *oxime* (*Roser*, Ann. **254**, 335) and an *anil*, which reacts with methyl iodide at room temperature to give a quaternary trimethylammonium iodide,  $C_8H_6O_3\left\langle\begin{array}{l}CH{:}NC_6H_5\\ C_2H_4N(CH_3)_3I\end{array}\right.$ (*Freund, Becker*, Ber. **36**, 1522). It also condenses with ketones and compounds containing a reactive methylene group with elimination of water; some of these condensation products, such as *anhydrocotarnineacetone*,  $C_8H_6O_3\left\langle\begin{array}{l}CH{:}CHCOCH_3\\ CH_2\cdot CH_2NHCH_3\end{array}\right.$, have an open structure, since they form benzoyl derivatives (*Kropf*, Ber. **37**, 2744). In the enol form cotarnine is reduced (*cf. Bandow, Wolffenstein*, Ber. **31**, 1577) to dihydrocotarnine (IV), and is oxidized by $KMnO_4$ to hydroxycotarnine (V) [*Wulf*, Bull.Acad.St.Petersburg [5], **11** (1900), 45; C. **1900, I,** 1029; *Freund, Wulff*, Ber. **35**, 1737]; both these products are true tetrahydroisoquinoline derivatives. On further oxidation hydroxycotarnine gives cotarnic acid, 4-methoxy-1,3-benzodioxole-5,6-dicarboxylic acid (VI), which yields 4-methoxy-1,3-benzodioxole-5-carboxylic acid when heated with hydrochloric acid, and gallic acid when heated with HI (*Roser*, Ann. **249**, 156; **254**, 334; **272**, 221; for the synthesis of cotarnic acid, see *Perkin, Robinson, Thomas*, J. **95**, 1977). Nitric acid oxidizes cotarnine to apophyllenic acid (VII), the methyl betaine of cinchomeronic acid (*cf. Koenigs, Wolff*, Ber. **29**, 2190). When boiled with dilute acetic acid, narcotine, like the cinchona alkaloids (p. 354), decomposes to a ketone, nornarceine (VIII), whose isonitroso derivative is split by the *Beckmann* rearrangement to hemipinic acid (X) and a nitrile (IX) (*Rabe, McMillian*, Ann. **377**, 223).



(I) Narcotine

(II) Cotarnine

(III) Meconine

(IV) Hydrocotarnine

(V) Cotarninol

(VI) Cotarnic acid

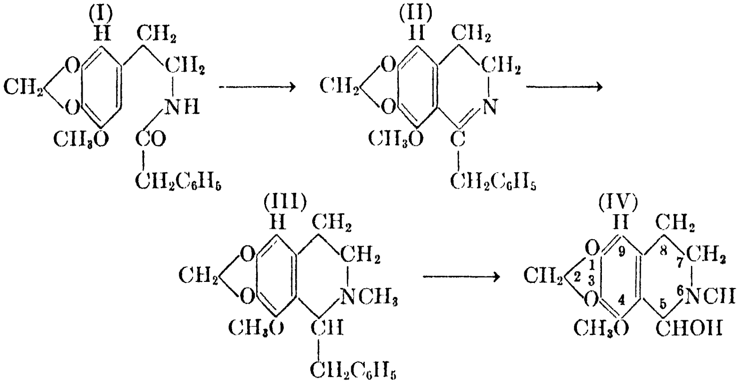
(VII) Apophyllenic acid

(VIII) Nornarceine

(IX)

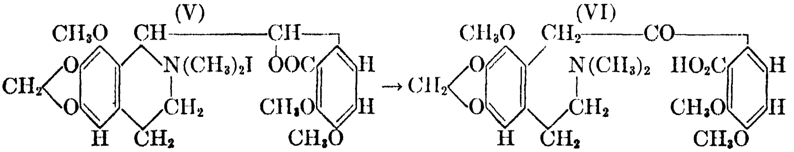
(X) Hemipinic acid

Synthesis of Cotarnine and Narcotine.—4-Methoxy-1,3-benzodioxole-6-propionic acid, $CH_3O[4]CH_2O_2\cdot C_6H_2[6]CH_2\cdot CH_2COOH$, prepared from myristicinealdehyde, $CH_3O[4]CH_2O_2\cdot C_6H_4[6]CHO$, by condensation with acetic ester, saponification and reduction, is converted by treatment of its amide with hypochloride to homomyristicylamine, 4-methoxy-6-β-aminoethyl-1,3-benzodioxole $CH_3O[4]CH_2O_2\cdot C_6H_2[6]CH_2CH_2NH_2$. The phenacyl derivative of this base (I) condenses when heated with P_2O_5 in xylene to 4-methoxy-5-benzyl-7,8-dihydro-1,3-dioxolo[*g*]isoquinoline (II), whose methyl iodide addition product is reduced by tin and hydrochloric acid to α-benzylhydrocotarnine (III). The latter is oxidized by manganese dioxide and dilute sulfuric acid, with simultaneous elimination of benzaldehyde, to cotarnine, 4-methoxy-6-methyl-5,6,7,8-tetrahydro-1,3-dioxolo[*g*]isoquinolinol-5 (IV) [*Salway*, J. **97**, 1208; *cf. Decker*, Chem.Ztg. **35** (1911), 1076]:

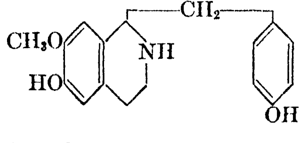


Cotarnine and meconine combine when boiled in methanol solution to form *dl*-narcotine or gnoscopine, whose resolution into *d*- and *l*-narcotine is mentioned above (*Perkin, Robinson*, J. **99**, 775). For the synthesis of β-gnoscopine, see *Hope, Robinson*, J. **105**, 2085.

Narceine (VI) $C_{23}H_{27}NO_8 + 3\,H_2O$, m.p. 170° (anhydrous), optically inactive is found together with narcotine in opium; it is formed from N-methylnarcotinium iodide (V) by treatment with aqueous potassium hydroxide [*Freund*, Ann. **286**, 248; *Frankforter, Keller*, Am.Chem.J. 22 (1899), 61]. See the analogous conversion of methylcinchoninium iodide to methylcinchotoxine, p. 355.



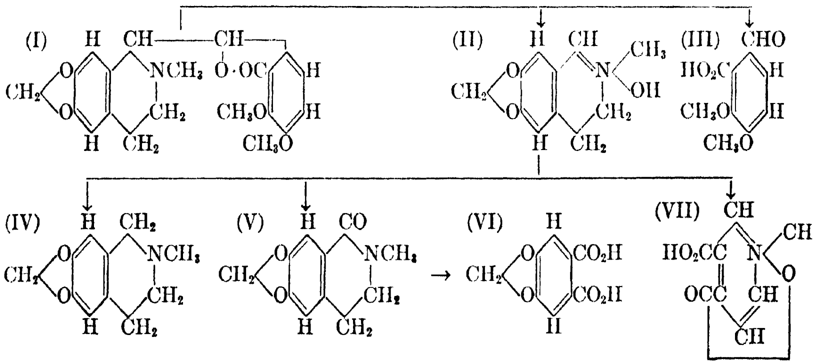
A simpler alkaloid of the benzylisoquinoline group is found in the Japanese species of *Cocculus*: **coclaurine**, $C_{10}H_{19}O_3N$, m.p. 221° [*Kondo, Kondo*, J.Pharm. Soc.Japan **48** (1929), 166]:



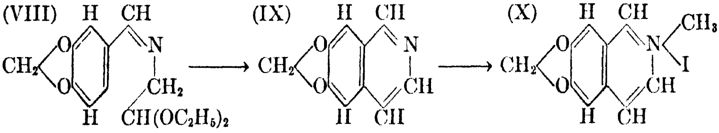
HYDRASTINE (I), $C_{21}H_{21}NO_6$ (see equations, p. 369), m.p. 132°, $[\alpha]_D$ −67° (chloroform) (*Durand*, 1851), occurs together with berberine (p. 372) in barberry, *Berberis vulgaris*, and in the root of *Hydrastis canadensis*, a North American plant belonging to the *Ranunculaceae* [*Gordin, Prescott*, Am.J.Pharm. **71** (1899), 257].

Hydrastine is similar in structure to narcotine, from which it differs only in having one methoxy group less. With oxidizing agents it decomposes into opianic acid (III) and *hydrastinine* (II), m.p. 116°, which is the cause of the *ergot*-like physiological action of hydrastine. Hydrastinine reacts like cotarnine (p. 366), partly as a cyclic alkamine, partly as an aminoaldehyde. By elimination of water it forms salts which are true dihydroisoquinolinium salts.

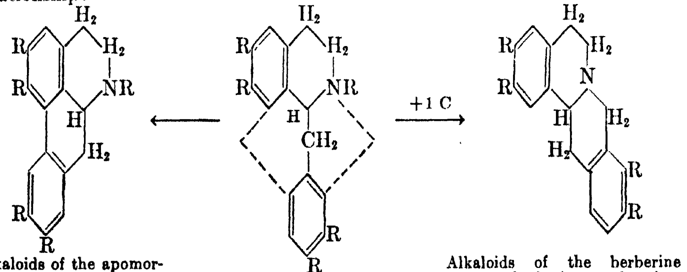
On reduction hydrastinine gives dihydrohydrastinine, 6-methyl-5,6,7,8-tetrahydro-1,3-dioxolo[*g*]isoquinoline (IV). When oxidized with potassium permanganate, hydrastinine first forms hydrastininol (V) and then hydrastinic acid, which rearranges with nitric acid to the methylimide of hydrastic acid, 1,3-benzodioxole-5,6-dicarboxylic acid (VI). For the synthesis of hydrastic acid, see *Perkin, Robinson*, J. **91**, 1073; *Oertly, Pictet*, Ber. **43**, 1336. Hydrastinine itself, like cotarnine, is oxidized by nitric acid to apophyllenic acid (VII) (*Roser*, Ann. **249**, 172; *Freund*, Ann. **271**, 311):



Synthesis of Hydrastinine.—Piperonalacetalamine (VIII) condenses in concentrated sulfuric acid to 1,3-dioxolo[*g*]isoquinoline (IX), whose methyl iodide addition product (X) is reduced by tin and hydrochloric acid to hydrohydrastinine (see IV, above), m.p. 60–61°. The latter is converted by potassium dichromate and sulfuric acid to hydrastinine (*Fritsch*, Ann. **286**, 18):



Laudanosine (p. 366), a derivative of 1-benzyl-1,2,3,4-tetrahydroisoquinoline, leads by a simple addition to its formula to two other polycyclic ring-systems which are the bases of a series of alkaloids. The following formulas show this relationship:

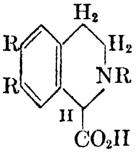


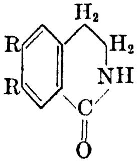
Alkaloids of the apomorphine group: apomorphine, bulbocapnine

Alkaloids of the berberine group: berberine, palmatine, jatrorrhizine, columbamine, corydaline, corytuberine

The characteristic products of the oxidation with $KMnO_4$ of apomorphine alkaloids, as derivatives of phenanthrene, are *8-phenanthrenecarboxylic acid,* and, on stronger oxidation, *mellophanic acid* (1,2,3,4-benzenetetracarboxylic acid), together with a corydaldinecarboxylic acid (I):

(I)

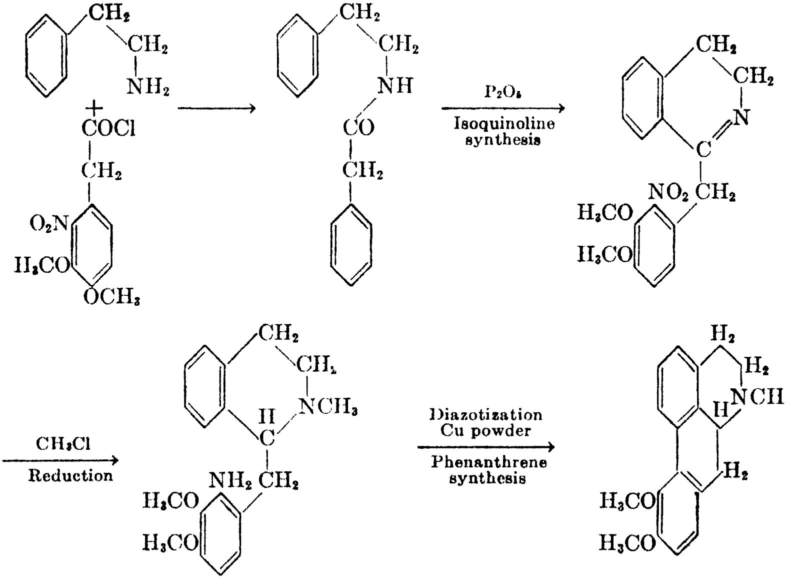




(II)

Alkaloids of the berberine group are converted by oxidation to *hemipinic acid* (3,4-dimethoxyphthalic acid) and *corydaldine* (II). The membership of an alkaloid in one of these groups (apomorphine or berberine) can generally be deduced from its oxidation products.

Apomorphine is mentioned among the reaction products of morphine on p. 359. Numerous members of the apomorphine group have been synthesized by a combination of the *Bischler* and *Napieralski* isoquinoline synthesis (Ber. **26,** 1903; see p. 250) and the *Pschorr* phenanthrene synthesis (Ber. **29,** 496). The course of such a synthesis for the dimethyl ether of apomorphine is given by the following equations (*Späth, Hromatka,* Ber. **62,** 325; *Haworth, Perkin, Rankin,* J. **127,** 2018; *Robinson, Shinoda,* J. **1926,** 2198):



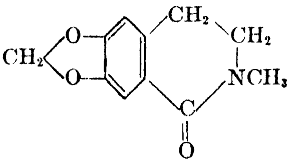
Apomorphine dimethyl ether

In this synthesis *2-nitrohomoveratroyl chloride* in benzene solution is converted by *phenethylamine* to the acid amide, which is condensed by P_2O_5 to an isoquinoline derivative. The methyl chloride addition product of 1-(*2-nitroveratryl*)-*3,4-dihydroisoquinoline* is reduced with tin and hydrochloric acid to the corresponding aminotetrahydroisoquinoline, which is condensed by the *Pschorr* phenanthrene ring formation to the *dimethyl ether of apomorphine.*

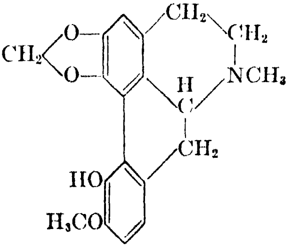
The same method has been used to prepare the dimethyl ether of *corytuberine* (*Späth, Hromatka,* Ber. **61,** 1692) and the dimethyl ether of *bulbocapnine* (*Gulland, Haworth,* J. **1928,** 1132; *Wessely, Demmer,* Ber. **61,** 1279).

In a few cases it is possible to prepare apomorphine compounds from 1-benzylisoquinoline derivatives by nitration and subsequent ring closure; see the conversion of laudanosine to glaucine (p. 372).

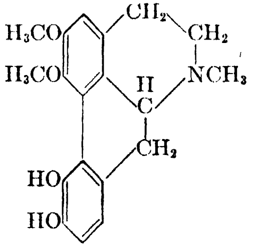
Bulbocapnine, $C_{19}H_{19}O_4N$, m.p. 199°, $[\alpha]_D$ +237°, is the principal alkaloid of the corydalis tubers. Unlike its associated alkaloids (see below), it belongs to the apomorphine group. Zinc dust distillation of its decomposition products yields 8-ethylphenanthrene, which is also obtained in the same way from apomorphine. Oxidative decomposition of bulbocapnine with $KMnO_4$ yields *hydrastininol* (I) while energetic oxidation with concentrated HNO_3 gives *mellophanic acid* (benzene-1,2,3,4-tetracarboxylic acid), which is the decomposition product of the phenanthrene nucleus of all apomorphine derivatives (*Späth, Holter, Posega,* Ber. **61,** 322):



(I) Hydrastininol



(II) Bulbocapnine



(III) Corytuberine

For the total synthesis of *d*-bulbocapnine methyl ether (m.p. 128–129°; $[\alpha]_D$ +259°) by the method shown above for the dimethyl ether of apomorphine, see *Gulland, Haworth,* J. **1928,** 1132; *Späth, Hromatka,* Ber. **61,** 1334.

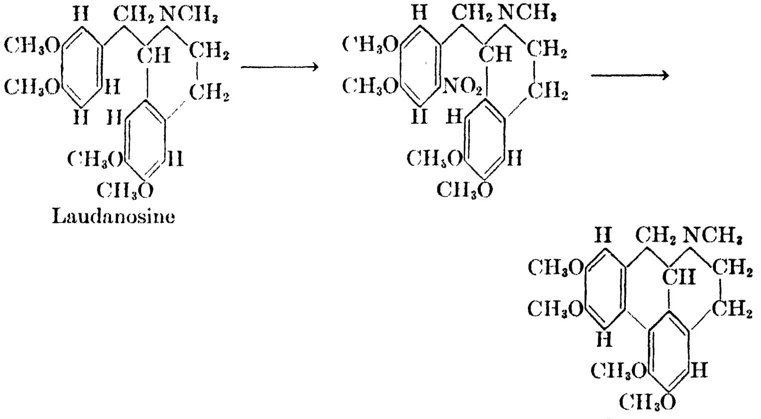
Corytuberine, $C_{19}H_{21}O_4N \cdot 5H_2O$, m.p. 240° (dec.), $[\alpha]_D$ +282.6° (alcohol), also occurring in the bulbs of *Corydalis cava,* is closely related to bulbocapnine (III, above). It contains two methoxy groups and two phenolic hydroxyl groups, and is converted by partial methylation to a mixture of:

Corydine, $C_{20}H_{23}O_4N$, m.p. 149° (dry), $[\alpha]_D$ +204.3° ($CHCl_3$) and

Isocorydine, $C_{20}H_{23}O_4N$, m.p. 185°, $[\alpha]_D$ +195.3°.

Glaucine, $C_{21}H_{25}O_4N$, m.p. 119–120°, $[\alpha]_D$ +113.3° (alcohol), is obtained from *Glaucium luteum.* Its constitution has been established by the conversion of *nitrolaudanosine* to *dl*-glaucine [*Gadamer,* Arch.Pharm. **249** (1911), 680].

The nitrolaudanosine resulting from nitration of laudanosine is reduced, diazotized and boiled with copper powder (see synthesis of phenanthrene, Vol. III, p. 668); the *dl*-glaucine so formed is resolved by means of tartaric acid to *d*- and *l*-glaucine. The dextrorotatory modification is identical with the naturally occurring glaucine.

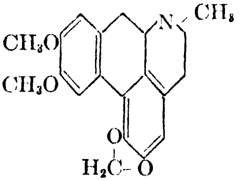


Laudanosine

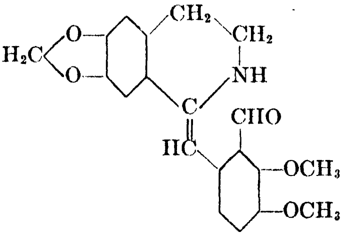
Glaucine

Glaucine is also prepared by methylation of **laurotetanine,** $C_{19}H_{21}O_4N \cdot H_2O$, m.p. 125°, $[\alpha]_D$ +98.5°, a secondary phenol-base of the apomorphine type. For its probable constitution, see *Späth, Strauhal,* Ber. **61,** 2395.

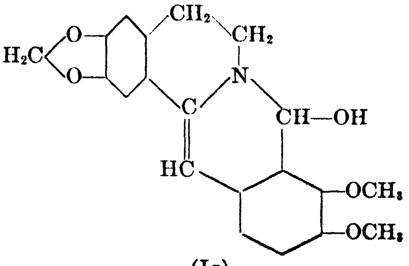
dl-**Dicentrine,** m.p. 169°, from *Dicentra pusilla,* is also a member of the apomorphine group, having the following formula [*Osada,* J.Pharm.Soc.Japan, **48** (1928), 85, 423]:



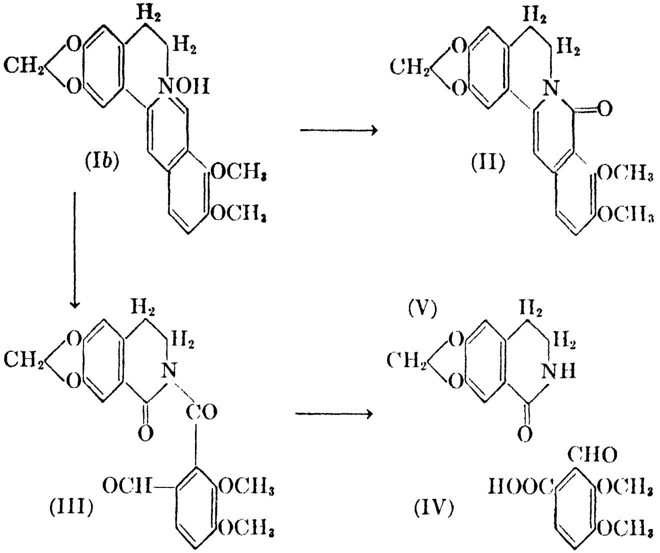
BERBERINE, $C_{20}H_{19}O_5N$, occurring in the roots of the barberry (*Berberis vulgaris*) and in many other plants, is the principal alkaloid of the berberine group. It exists in an ammonium form (formula I*b* on p. 373) (*berberinium hydroxide*), stable only in aqueous solution, and in a yellow form insoluble in water, m. p. 144°, for which formula I (*berberinal*) and formula I*a* (*berberine* or *berberinol*) has been suggested (*Gadamer,* Arch. Pharm. **243,** 31; *Tinkler,* J. **99,** 1340; *Perkin,* J. **113,** 504). Berberine is optically inactive. Oxidation with $KMnO_4$ yields among other compounds "*hydroxyberberine*" (II) and *berberal* (III). The latter is decomposed by boiling dilute H_2SO_4 to pseudoopianic acid (IV) and 6,7-methylenedioxy-3,4-dihydro-1(2)-isoquinolone (V) (*Perkin,* J. **55,** 63; **57,** 992; *Schmidt,* Arch. Pharm. **225,** 168). "Phenyldihydroberberine" from berberine and C_6H_5MgBr yields 2-benzoyl-3,4-dimethoxybenzoic acid with $KMnO_4$ (*Faltes,* Mo. **31,** 557).



(I)

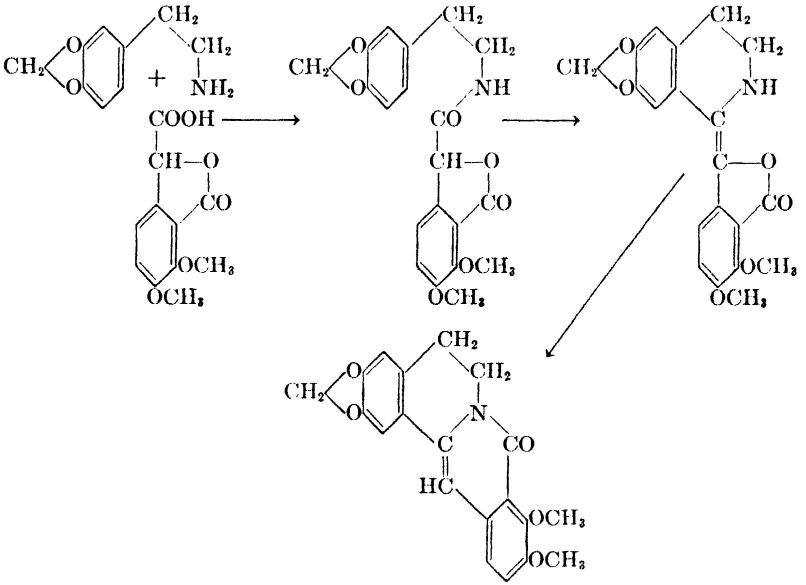


(I*a*)



(Ib) (II) (III) (IV) (V)

As an amino aldehyde berberine forms an oxime with hydroxylamine and a *p*-dimethylaminoanil with *p*-dimethylaminoaniline [*Gadamer*, Arch.Pharm. **243** (1905), 31]; it condenses with ketones with elimination of water (see the derivative with acetone: *Pyman*, J. **99**, 1690). When warmed with alkali berberine yields "*dihydroberberine*" and "*hydroxyberberine*" (II, above). Berberine has affinity for fibers. It forms yellow-brown needles. On reduction it gives the colorless "*tetrahydroberberine*," $C_{20}H_{21}NO_4$, the racemic form of **canadine**, which is



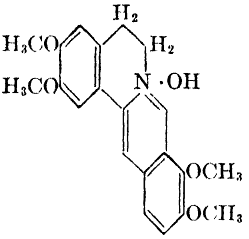
Hydroxyberberine

found together with hydrastine in the root of *Hydrastis canadensis*. With the aid of bromocamphorsulfonic acid, tetrahydroberberine can be resolved into *d*- and *l*-canadine [*Voss, Gadamer*, Arch.Pharm. **248** (1910), 43]. When berberine hydrochloride is heated at 200° in a current of CO_2, methyl chloride is split off and a dark red phenolbetaine, *berberubin*, $C_{19}H_{15}NO_4$, is produced; berberine hydriodide is regenerated from this by the action of methyl iodide [*Frerichs*, Arch.Pharm. **248** (1910), 276; constitution of berberubin: *Späth, Burger*, Ber. **59**, 1488].

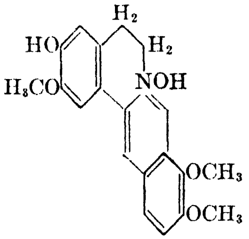
The complete synthesis of berberine has been accomplished by the preparation of hydroxyberberine (*Späth, Quietensky*, Ber. **58**, 2268; *Perkin, Rây, Robinson*, J. **127**, 740) (see p. 373).

The alkaloids of the calumba root are similar in structure to berberine (preparation of the alkaloids: *Späth, Duschinsky*, Ber. **58**, 1942; *Späth, Polgar*, Mo. **52**, 117). **Palmatine**, $C_{21}H_{22}O_4N(OH)$, iodide m.p. 240°, is converted by reduction to the characteristic tetrahydropalmatine, $C_{21}H_{25}O_4N$, m.p. 144°, which is found in its *d*-form in corydalis tubers (*Späth, Mosettig, Tröthandl*, Ber. **56**, 875; *Späth, Mosettig*, Ber. **59**, 1496). **Jatrorrhizine**, $C_{20}H_{20}O_4N(OH)$, iodide, m.p. 208–210°; the nitrate, m.p. 225° (dec.), can be reduced to tetrahydrojatrorrhizine, which occurs in its *dl*-form, known as corypalmine, in the tubers of *Corydalis cava* (see below). With these two bases, a third, **columbamine**, isomeric with jatrorrhizine is found in small quantities (*Späth, Burger*, Ber. **59**, 1486).

Palmatine has been found to have the following constitution, which is similar to berberine [*Feist, Sandstede*, Arch.Pharm. **256** (1918), 1].



(I) Palmatine



(II) Jatrorrhizine

The formula of palmatine has been determined by the results of the oxidative decomposition. *Berberine* can be converted into *palmatine* or *tetrahydropalmatine* (*Späth, Lang*, Ber. **54**, 3064; *Späth, Quietensky*, Ber. **58**, 2269). For the complete synthesis of *d*-tetrahydropalmatine from berberine, see *Späth, Mosettig*, Ber. **59**, 1497. When palmatine is heated alone, a methyl group is eliminated, leaving a red phenolbetaine, *palmatrubin* (constitution: *Späth, Burger*, Ber. **59**, 1489), analogous to the berberubin from berberine.

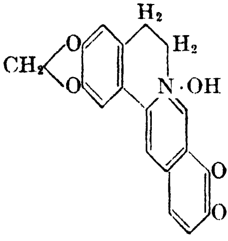
Jatrorrhizine (II) is the phenol-base corresponding to palmatine (*Späth, Duschinsky*, Ber. **58**, 1939), to which it is converted by methylation with diazomethane.

For the constitution of *columbamine*, see *Späth, Burger*, Ber. **59**, 1486.

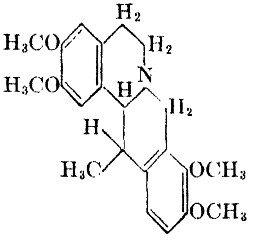
A structure similar to that of the alkaloids of the calumba root is found in several bases of the larkspur tubers (*Corydalis cava, Bulbocapnus cavus*). The versatility of plant synthesis is demonstrated in this species. The same plant contains bases of the apomorphine group (bulbocapnine is the principal alkaloid) and others of the berberine or protopine type. Bulbocapnine has been described on p. 371. Those of the berberine type include:

Corydaline, $C_{22}H_{27}O_4N$, m.p. 134°, $[\alpha]^{20}_{D}$ +300°; **corybulbine**, $C_{21}H_{25}O_4N$, m.p. 237°, $[\alpha]_D$ +303°; **isocorybulbine**, m.p. 180°, $[\alpha]_D$ +299.8°; *d*-**tetrahydropalmatine**, $C_{21}H_{25}O_4N$, m.p. 142°, $[\alpha]_D$ +292.5° (*Späth, Mosettig, Tröthandl*, Ber. **56**, 877); *d*-**tetrahydrojatrorrhizine** = **corypalmine**, $C_{21}H_{25}O_4N$, m.p. 236°, $[\alpha]^{18}_{D}$ +280°.

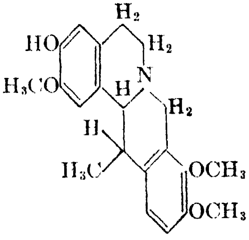
These alkaloids are derivatives of tetrahydroberberine. This relationship is shown by a comparison of the formulas of berberine and corydaline:



Berberine



Corydaline



Corybulbine

The constitution of corydaline has been established chiefly from the products of oxidation with $KMnO_4$ (*Späth, Dobrowsky*, Ber. **58**, 1274). This structure is supported by the formation of *dl-corydaline* by reduction of the product obtained by introduction into palmatine (after protecting the nitrogen atom with acetone) with CH_3I of the additional methyl group which is present in corydaline [*v. Bruchhausen*, Arch.Pharm. **259** (1923), 245]. *Corybulbine* and *isocorybulbine* are the corresponding phenol-bases (see formula).

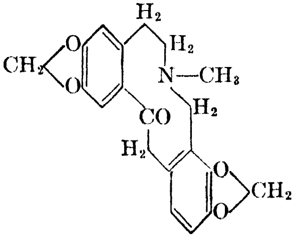
Methylenepapaverine can also be converted into *corydaline* (*Späth, Kruta*, Ber. **62**, 1024).

PROTOPINE ALKALOIDS

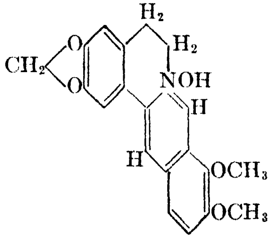
Some of the bases of the protopine type have been found in opium, and some as subsidiary alkaloids in the corydalis root. The determination of their constitution is due to the investigations of *W. H. Perkin* (J. **109**, 815). The following alkaloids are characteristic of the group:

Protopine, $C_{20}H_{19}O_5N$, m.p. 208°, optically inactive, was first isolated from opium and later from other plants, especially *Dicentra spectabilis*. It contains two methoxy groups. **Cryptopine**, $C_{21}H_{23}O_5N$, m.p. 219°, a subsidiary alkaloid of morphine, contains one methylenedioxy group and two methoxy groups. **Corycavine**, $C_{21}H_{21}O_5N$, m.p. 222°, optically inactive [*Gadamer, v. Bruchhausen*, Arch.Pharm. **260** (1922), 97], and its optically active form, **corycavamine** (*Späth, Holter*, Ber. **60**, 1893), have been isolated from the corydalis root.

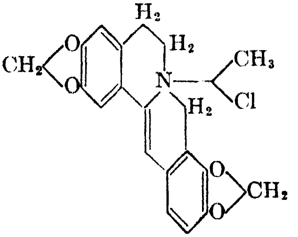
A comparison of the formulas of protopine and berberine shows the similarity between these two types of alkaloids:



(I) Protopine



(II) Berberine



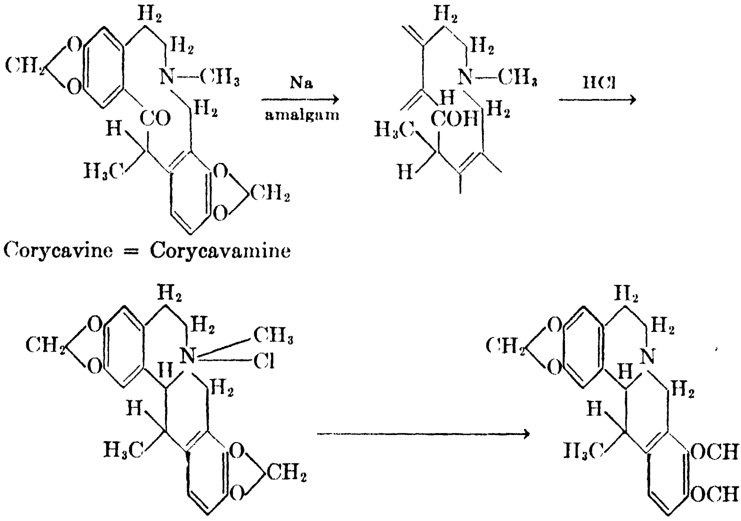
(III) Isoprotopine chloride

In the protopine type the formation of the isoquinoline group by the plant is incomplete. The 10-membered ring in protopine and alkaloids of similar structure readily "constricts" to form two 6-membered rings. This reaction, discovered by *W. H. Perkin*, occurs in the presence of $POCl_3$; in this way protopine is converted into *isoprotopine chloride* (Formula III, above) (*Perkin*, J. **109**, 815; **115**, 713). The condensation occurs even more readily (by evaporation with hydrochloric acid) with the dihydro derivatives of protopine (see the section on the conversion of corycavine to *dl*-corydaline).

Cryptopine has a structure like protopine, except that the methylenedioxy (dioxolo) group is replaced by two methoxy groups. Similarly to protopine, it is converted by $POCl_3$ to isocryptopine chloride.

For the synthesis of protopine and cryptopine, see *Haworth, Perkin,* J. **1926**, 1769.

Corycavine and its optically active form, *corycavamine*, contain a methyl group on a carbon atom. Corycavine is directly related to *corydaline* (p. 375), being converted into its *dl*-modification by "constriction of the 10-membered ring" (*Späth, Holter,* Ber. **60**, 1891). This important transition is given by the following equations:



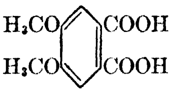
Corycavine = Corycavamine

dl-Corydaline

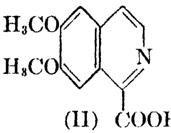
A group of alkaloids having a more complicated structure, but known to contain an isoquinoline ring, are isolated from ipecac (*Psychotria ipecacuanha*). Their complete constitution has not yet been determined.

Emetine, $C_{29}H_{40}O_4N_2$, amorphous powder, m.p. 74°, $[\alpha]_D$ about $-30°$ (aqueous alcohol); **cephaeline,** $C_{28}H_{38}O_4N_2$, m.p. 120–130° (dried), $[\alpha]_D$ $-43.4°$ ($CHCl_3$); **psychotrine,** $C_{28}H_{36}O_4N_2 \cdot 2\,H_2O$, m.p. 138° after sintering at 120°; **O-methylpsychotrine** $C_{29}H_{36}O_4N_2$, amorphous, $[\alpha]_D$ $+43.9°$ (alcohol); **emetamine,** $C_{29}H_{36}O_4N_2$, m.p.155–156°, $[\alpha]_D$ $+9.9°$ ($CHCl_3$).

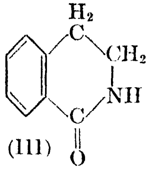
These alkaloids are closely related among themselves, as their molecular formulas indicate. Emetine is O-methylcephaeline (*Karrer*, Ber. **49**, 2065). Catalytic hydrogenation converts the psychotrines to emetine and cephaeline (*Pyman*, J. **111**, 419; *Karrer*, Ber. **49**, 2057). Emetine and O-methylpsychotrine contain four methoxy groups, while cephaeline and psychotrine, the corresponding phenol-bases, contain three methoxy groups and one OH-group. One of the nitrogens is a secondary one, and the other is tertiary. The presence of the isoquinoline ring was determined by oxidation with $KMnO_4$ in acetone, which produced *m-hemipinic acid* (I) and 6,7-*dimethoxyisoquinoline*-1-*carboxylic acid* (II) (*Pyman*, J. **111**, 419; *Windaus, Hermanns,* Ber. **47**, 1470):



(I)



(II)



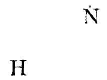
(III)

Under somewhat different conditions ($KMnO_4$ in slightly alkaline solution), hemipinic acid and *corydaldine* (III) are obtained; this indicates the presence of a tetrahydroisoquinoline ring in the alkaloids oxidized. According to the quantitative analysis of the oxidation products each alkaloid contains two isoquinoline rings (*Späth*, *Leithe*, Ber. **60**, 692). For the exhaustive methylation of emetine, see *Karrer*, Ber. **49**, 2073; for the *Emde* decomposition, see *Späth*, Ber. **60**, 702.

For a proposed formula for emetine, see *Staub*, Helv. **10**, 826.

VII. ALKALOIDS OF THE INDOLE GROUP

The alkaloids of the indole group are derivatives of norharman, 9-pyrid[3,4-*b*]indole:



Derivatives of this ring system have been found in *Peganum harmala*. They are:

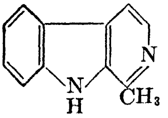
Harmaline, $C_{13}H_{14}ON_2$, m.p. 250° (dec.), optically inactive (*Manske*, *Perkin*, *Robinson*, J. **1927**, 1); **harmine**, $C_{13}H_{12}ON_2$, m.p. 264–265° (*Lawson*, *Perkin*, *Robinson*, J. **125**, 626). When digested with hydrochloric acid, the latter yields **harmalol**, $C_{12}H_{12}ON_2$, m.p. 212° (dec.), and **harmol**, m.p. 321°.

Harmine is identical with *banisterine* from *Banisteria caapi* (*Elger*, Helv. **11**, 162; *Mayer*, Chem.Ztg. **1930**, Fortschrittsber. p. 4).

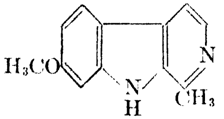
Harmaline and harmine contain a secondary and a tertiary nitrogen atom; the oxygen atom is present in a methoxy group, from which the methyl group can be split by boiling with concentrated hydrochloric acid, thereby forming the phenol-bases *harmalol* and *harmol*. *Harmaline* is *dihydroharmine;* both bases give the same tetrahydroharmine when further reduced.

The clarification of the basic ring structure of these alkaloids is due to the work of *O. Fischer*, *Perkin* and *Robinson*. A great advance in this difficult problem was the discovery that **harman** (I), the base obtained from harmine by elimination of the methoxy group, is identical with a compound prepared by *Hopkins* and *Cole* by the oxidation of tryptophan with $FeCl_3$ (see pp. 67, 266).

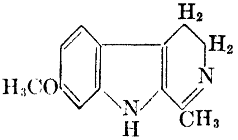
This information, together with the results of the oxidative decomposition—formation of *m*-nitroanisic acid and isonicotinic acid (4-pyridinecarboxylic acid)—led to the accompanying formulas for harmine and harmaline:



(I) Harman



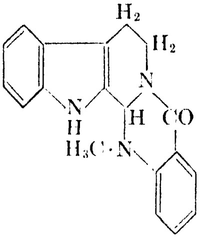
(II) Harmine = banisterine
(*Lawson, Perkin, Robinson*, J. **125,** 626)



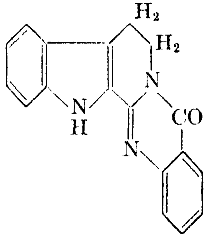
(III) Harmaline
(*Manske, Perkin, Robinson*, J. **1927,** 1)

The synthesis of the harman structure is covered in an earlier section (p. 266)

Evodiamine (IV), $C_{19}H_{17}ON_3$, m.p. 278°, $[\alpha]_D$ +352°, and **rutaecarpine** (V), $C_{18}H_{13}ON_3$, isolated from *Evodia rutaecarpa*, have the following constitution:



(IV) Evodiamine



(V) Rutaecarpine

For their synthesis, see *Asahina, Ohta*, Ber. **61,** 319; *Asahina, Manske, Robinson*, J. **1927,** 1708.

VIII. ALKALOIDS OF THE IMIDAZOLE GROUP

A group of alkaloids which are derivatives of imidazole are found in the South American jaborandi leaves (isolation from the leaves: *Chemnitius*, J.pr. **118,** 20). Among these are:

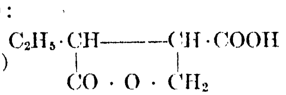
Pilocarpine, $C_{11}H_{16}N_2O_2$, m.p. 34°, $[\alpha]_D$ +101.6°, b.p. 266° (5 mm.) (*Pinner, Schwarz*, Ber. **35,** 209); hydrochloride, m.p. 204°, from *Pilocarpus jaborandi*. **Isopilocarpine,** $C_{11}H_{16}N_2O_2$, b.p. 261° (10 mm.), $[\alpha]_D$ +42.8°; hydrochloride, m.p. 159° (anhydrous), together with pilocarpine from *Pilocarpus microphyllus* or from pilocarpine by heating alone or with alcoholic NaOH; it is apparently stereoisomeric with pilocarpine. **Pilocarpidine,** $C_{10}H_{14}N_2O_2$, $[\alpha]_D$ +81.3°; nitrate, m.p. 137°, from *Pilocarpus microphyllus*. **Pilosine,** $C_{16}H_{18}O_3N_2$, m.p. 187°, $[\alpha]_D$ +39.9° (*Pyman*, J. **101,** 2260).

Pilocarpine contains one N-methyl group, which is lacking in pilocarpidine. When isopilocarpine is oxidized with $KMnO_4$, an aliphatic side chain is split off in the form of two lactone-carboxylic acids:

Pilopic acid, $C_7H_{10}O_4$, m.p. 104°, $[\alpha]_D$ +36.1°.

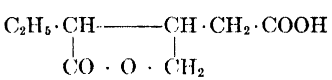
Homopilopic acid, $C_8H_{12}O_4$, b.p. 235° (20 mm.).

The structure of these two acids (Formulas I and II) is established by the formation of *n*-butyric acid from pilopic acid and 2-ethyltricarballylic acid from homopilopic acid on fusion with KOH. Pilopic acid has also been synthesized and resolved into its optical antipodes (*Tschitschibabin, Preobrashensky*, Ber. **63,** 460):

(I)


$$\begin{array}{ccc} C_2H_5\cdot CH & \text{———} & CH\cdot COOH \\ | & & | \\ CO & \cdot\ O\ \cdot & CH_2 \end{array}$$

Pilopic acid

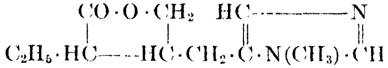

(II)

$$\begin{array}{ccc} C_2H_5\cdot CH & \text{———} & CH\cdot CH_2\cdot COOH \\ | & & | \\ CO & \cdot\ O\ \cdot & CH_2 \end{array}$$

Homopilopic acid

Information concerning the second section of the pilocarpine alkaloids is obtained from the distillation with soda lime; the product is 1,5-*dimethylimidazole*

(*Pyman*, J. **121**, 2616). This establishes the position if the link is between the two sections of the molecule (the 5-position of the imidazole ring). These experimental results are expressed in the following formula for pilocarpine:



Pilocarpine (Isopilocarpine)

Pilocarpine contains the lactone bridge found in its two acid decomposition products. This explains the ease of conversion of pilocarpine with alkalis to *pilocarpoic acid*, which is richer by 1 H_2O.

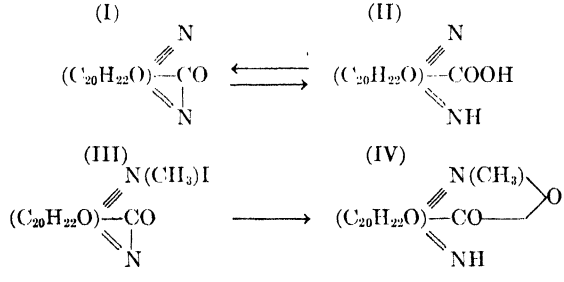
Pilocarpidine is the N-methyl-free secondary base corresponding to pilocarpine (*Späth, Kunz*, Ber. **58**, 513).

The alkaloids of the jaborandi leaves are sudorific agents; pilocarpine is therefore opposite in behavior to atropine and adrenaline.

IX. IMPORTANT ALKALOIDS OF UNKNOWN STRUCTURE

STRYCHNOS BASES. In the nux vomica, the seeds of *Strychnos nux vomica*, and in the St. Ignatius' bean (*Strychnos ignatii*) there are found two very poisonous bases, strychnine and brucine (discovered in 1818 and 1819 by *Pelletier* and *Caventou*), together with a subsidiary alkaloid, vomicine (see below). In spite of numerous investigations, the constitution of these alkaloids is still in doubt.

STRYCHNINE, $C_{21}H_{22}N_2O_2$, m.p. 268°, b.p. 270° (5 mm.), $[\alpha]_D$ −132° (alcohol), reacts alkaline, has a very bitter taste and causes tetanus. It is colored an intense blue-violet by a solution of chromic acid in sulfuric acid. Strychnine is an unsaturated, monoacid, tertiary amine; it adds alkyl halides (*Moufang, Tafel*, Ann. **304**, 49). The second N-atom is held in a lactam bridge with a CO-group; this follows from the conversion of strychnine (I) by warming with sodium alcoholate solution to *strychnic acid* (II), $C_{21}H_{24}N_2O_3$, m.p. 215°, which regenerates strychnine when boiled with acids. With moist silver oxide the *methyl iodide addition product of strychnine* (III) yields *methylstrychnine* (IV), which is the *methylbetaine of strychnic acid*, since it is also formed from the silver salt of the methyl iodide addition product of strychnic acid. In this reaction the bond of the carboxyl group shifts from one nitrogen atom to the other, from a lactam group to a betaine group:

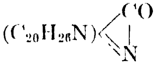


When heated with water at 160–180°, strychnine rearranges to an isomeric base, *isostrychnine*, m.p. 224°, which, like strychnine, is converted by warm sodium alcoholate solution to an acid, *isostrychnic acid*, m.p. 231° (*Bacovescu, Pictet*, Ber. **38**, 2787; *Leuchs, Nitschke*, Ber. **55**, 3171; *Oxford, Perkin, Robinson*, J. **1927**, 2389), and yields, with methylating agents, methylisostrychnine.

The first product of the reduction of strychnine with hydrogen and colloidal palladium is a *dihydrostrychnine*, $C_{21}H_{24}N_2O_2 \cdot 2\,H_2O$, m.p. 222° (anhydrous) (*Knorr, Hess*, Ber. **44**, 2863; *Oxford, Perkin, Robinson*, J. **1927**, 2389). With hydriodic acid and phosphorus, *desoxystrychnine* (V), which also contains a lactam group, is formed. Electrolytic reduction of strychnine gives *tetrahydrostrychnine*

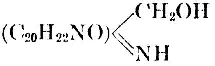
(VI), m.p. 202°, or a compound containing one H_2O less, *strychnidine* (VII), m.p. 246°, in which the lactam group is reduced (*Tafel, Naumann*, Ber. **34**, 3291; *Leuchs*, Ber. **47**, 536; *Clemo, Perkin, Robinson*, J. **1927**, 1589; oxidative decomposition of strychnidine: *Leuchs, Krohnke*, Ber. **63**, 1045). On further reduction the second oxygen atom, which has been assigned an ether function (*Fawcett*,

(V)



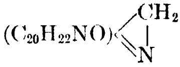
$$(C_{20}H_{26}N){<}\begin{matrix}CO\\ |\\ N\end{matrix}$$

(VI)



$$(C_{20}H_{22}NO){<}\begin{matrix}CH_2OH\\ \\ NH\end{matrix}$$

(VII)

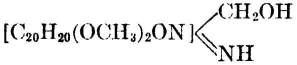


$$(C_{20}H_{22}NO){<}\begin{matrix}CH_2\\ |\\ N\end{matrix}$$

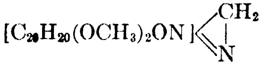
Perkin, Robinson, J. **1928**, 3082), is also eliminated, and *dihydrostrychnoline*, $C_{21}H_{28}N_2$, and *strychnoline*, $C_{21}H_{26}N_2$, are produced. Reaction products of strychnine which no longer contain a lactam ring correspond in behavior to tetrahydroquinolines (p. 244). The action of nitric acid on strychnine yields various nitro derivatives (*Leuchs, Kröhnke*, Ber. **62**, 2176) and, finally, picric acid, 3,5-dinitrobenzoic acid, m.p. 204°, and 6,8-*dinitrodihydroxyquinolinecarboxylic acid*, m.p. 295–300° (*Tafel*, Ann. **301**, 2851; *Menon, Perkin, Robinson*, J. **1930**, 830). Oxidation of strychnine with permanganate in alkaline solution gives N-*oxalylanthranilic acid*, m.p. 203° (*Späth, Bretschneider*, Ber. **63**, 2997); similar treatment in acetone solution produces *strychninonic acid*, $C_{21}H_{20}O_6N_2$, a dibasic oxocarboxylic acid, which is reduced by sodium amalgam to the corresponding hydroxycarboxylic acid, *strychninolic acid*, $C_{21}H_{22}O_6N_2$. The latter decomposes in dilute alkali even at room temperature to glycolic acid and the neutral *strychninolone*, $C_{19}H_{18}O_3N_2$ (*Leuchs, Reich*, Ber. **43**, 2417). When warmed with hydrogen peroxide, strychnine is oxidized to *strychnine oxide*, $C_{21}H_{22}N_2O_3$, and *strychnine peroxide*, $C_{21}H_{22}N_2O_4$, which regenerate strychnine with loss of oxygen (*Pictet, Mattisson*, Ber. **38**, 2782; *Mossler*, Mo. **31**, 329). With MnO_2 and sulfurous acid strychnine forms three isomeric *strychninemonosulfonic acids*, $C_{21}H_{21}O_2N_2(SO_3H)$, which can be separated by means of their different solubilities in water (*Leuchs, Schneider*, Ber. **42**, 2681). Chromic acid oxidation converts strychnine and diaminostrychnine to two oxo-dicarboxylic acids: $C_{17}H_{22}N_2O_6 \cdot 5\,H_2O$ and $C_{16}H_{20}N_2O_4$, which are also obtained from brucine (see below).

BRUCINE, $C_{21}H_{20}(OCH_3)_2N_2O_2 + 4\,H_2O$, m.p. 178° (anhydrous), $[\alpha]_D$ $-119°$, has an effect similar to strychnine, but feebler. In its chemical behavior, it resembles strychnine closely. It contains two methoxy groups, and has been proved to be dimethoxystrychnine, the two methoxy groups being *ortho* to one another on an aromatic ring (*Lions, Perkin, Robinson*, J. **127**, 1158; *Späth, Bretschneider*, Ber. **63**, 2997). Like strychnine, it is converted by sodium alcoholate to an acid, *brucic acid*, $C_{20}H_{21}(OCH_3)_2N_2O(COOH)$, m.p. 245°, which regenerates brucine when boiled with water. The action of methyl iodide on brucine or brucic acid is completely analogous to that on strychnine. Hydrogen and colloidal palladium reduce brucine to *dihydrobrucine*, $C_{23}H_{28}O_4N_2$, m.p. 179–181° (anhydrous), while electrolytic reduction yields *tetrahydrobrucine* (I), m.p. 177°, and *brucidine* (II), m.p. 203° (*Moufang, Tafel*, Ann. **304**, 24; *Gulland, Perkin, Robinson*, J. **1927**, 1627).

(I)



$$[C_{20}H_{20}(OCH_3)_2ON]{<}\begin{matrix}CH_2OH\\ \\ NH\end{matrix}$$



$$[C_{20}H_{20}(OCH_3)_2ON]{<}\begin{matrix}CH_2\\ |\\ N\end{matrix}$$

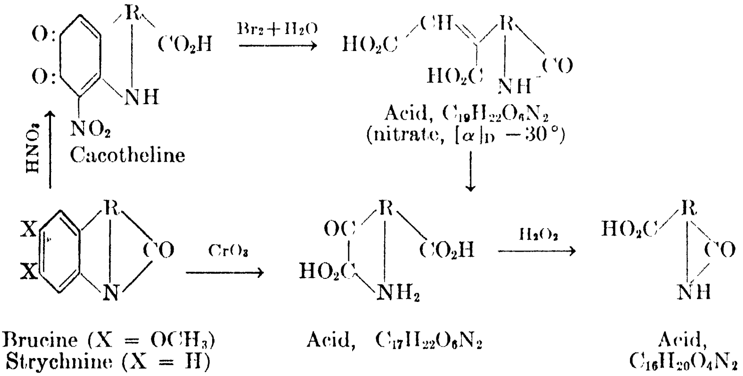
(II)

Compounds (I) and (II) can be reduced catalytically to **hexahydrobrucine**, m.p. 131–133°, or to **dihydrobrucidine**, m.p. 172.5° (*Achmatowicz, Fawcett, Perkin, Robinson*, J. **1930**, 1739).

Fusion of dihydrobrucine with alcoholic KOH yields **dihydrobrucine hydrate,** $C_{23}H_{30}O_5N_2$, m.p. 240° (dec.), $[\alpha]_D$ $-183.7°$ (*Wieland, Gumlich*, Ann. **482**, 50).

Brucine is oxidized by permanganate in alkaline solution to 4,5-*dimethoxy*-N-*oxalylanthranilic acid*, m.p. 230–232° (*Späth, Bretschneider*, Ber. **63**, 2997); in acetone solution it is oxidized to *brucinonic acid*, $C_{23}H_{24}O_8N_2$ (*Leuchs, Gladkorn*, Ber. **56**, 1780), which, analogously to strychninonic acid (see above), can be converted to *brucinolic acid*, $C_{23}H_{26}O_8N_2$ and *brucinoline*, $C_{21}H_{22}O_5N_2$ (*Leuchs, Weber*, Ber. **42**, 3703; *Leuchs, Rauch*, Ber. **46**, 3917; *Leuchs, Gladkorn, Hellriegel*, Ber. **56**, 2472). With hydrogen peroxide brucine gives *brucine oxide*, $C_{23}H_{26}N_2O_5$, and *brucine peroxide*, $C_{23}H_{26}N_2O_6$. With MnO_2 and sulfurous acid four isomeric brucinemonosulfonic acids, $C_{23}H_{25}N_2O_4(SO_3H)$ (*Leuchs, Geiger*, Ber. **44**, 3049; *Leuchs, Zander*, Ber. **56**, 502). Brucine dissolves in concentrated nitric acid with a red color, which turns yellow when the solution is warmed and violet when stannous chloride is added. These color changes are due first to the demethylation and oxidation of brucine to a red *quinone*, $C_{21}H_{20}O_4N_2$, m.p. 295°, and then to conversion of the latter by nitric acid, with simultaneous nitration, to the yellow *cacotheline*, $C_{21}H_{21}N_7O_3$. Reduction of the quinone with sulfurous acid produces the demethylated brucine, $C_{21}H_{20}(OH)_2N_2O_2$ (*Leuchs, Anderson*, Ber. **44**, 2136; **44**, 3040). Cacotheline is converted by bromine water to an oxo-dicarboxylic acid, $C_{19}H_{22}O_6N_2$ (*Sucharda*, Ber. **58**, 1729), which can be further oxidized into the same C_{17} and C_{16} acids which are obtained from brucine by oxidation with chromic acid. From this oxidation of brucine two oxo-carboxylic acids, $C_{17}H_{22}N_2O_6 \cdot 5\,H_2O$, $[\alpha]_D$ +49.2° (water), and $C_{16}H_{20}N_2O_4$, m.p. 312°, $[\alpha]_D$ −116° (water), have been isolated (*Wieland, Münster*, Ann. **469**, 216). These same acids are formed in the oxidation of strychnine (*Triebs*, Ann. **476**, 28) and mono- and diaminostrychnine (*Leuchs, Kröhnke*, Ber. **62**, 2176) with chromic acid; this is a proof of the similarity of the two alkaloids. In both acids the aromatic rings of the alkaloids are disintegrated.

The most important decomposition reactions of the two alkaloids are summarized in the following equations, in which the unaffected portion, $C_{14}H_{18}ON$, of the molecule is designated as R:



Cacotheline

Acid, $C_{19}H_{22}O_6N_2$ (nitrate, $[\alpha]_D$ −30°)

Brucine (X = OCH_3)
Strychnine (X = H)

Acid, $C_{17}H_{22}O_6N_2$

Acid, $C_{16}H_{20}O_4N_2$

Strychnidine has been subjected to similar decomposition reactions (*Leuchs, Kröhnke*, Ber. **63**, 1045).

Proposed structural formulas for strychnine and brucine: *Fawcett, Perkin, Robinson*, J. **1928**, 3082; *Menon, Perkin, Robinson*, J. **1930**, 830.

Vomicine, $C_{22}H_{24}N_2O_4$, m.p. 182° (dec.), $[\alpha]_D$ +80.4° (alcohol), hydrochloride m.p. 245° (dec. and discoloration) (*Wieland, Oertel*, Ann. **469**, 193), is found in the residual liquor from the other two strychnos alkaloids, to which it is very similar in chemical behavior. Like these, it is a monoacid, tertiary base; one of the four oxygen atoms is in a lactam group (proved by the conversion in alkaline solution to *vomicinic acid*, sensitive to air), another is in a tertiary (?) alcohol group, and a third is an ether oxygen atom. The fourth is connected to an aromatic ring. A characteristic property of vomicine is the green coloration when it is boiled with KOH in methanol; acidification with hydrochloric acid and addition of ferric chloride changes the color to red-violet. For the reduction with hydriodic acid and the oxidation with CrO_3, see *Wieland, Oertel*, Ann. **469**, 197, 199.

YOHIMBEHE ALKALOIDS. The group of yohimbehe alkaloids is also of unknown constitution. The most important member, **yohimbine**, was discovered in 1896 by *Spiegel* (*Thoms*, Ber. **7**, 279) in the bark of *Corynanthe yohimbe* Schumann. Since the recognition of its various physiological effects, it has been used in pharmacological practice as juvenine, johimpava, etc. The extensive use of the drug, as well as the bark extracts from *Pausinystalia yohimbe* Pierre and *Cortex Quebracho blanco*, has led to the discovery of numerous isomers and related compounds, which are given in the accompanying table.

Alkaloid, $C_{21}H_{26}N_2O_3$	M.p. (dec.), °C.	$[\alpha]_D$	Hydrochloride, m.p. (dec.), °C.
Yohimbine	278	43.7°	234
Alloyohimbine	135–140	−72.7	279
Isoyohimbine	239–240	99	298
α-Yohimbine	235	−9.3	286
β-Yohimbine	216	94.8	295
γ-Yohimbine	240	−28.3	312
Quebrachine	234–235	107.9	282
Corynanthine	242	−125	285–290
Alkaloid, $C_{20}H_{24}N_2O_3$	M.p. (dec.), °C.	$[\alpha]_D$	
Yohimbenic acid	230	−17.1°	
Alloyohimbic acid	248–250	−79.5	
Isoyohimbic acid	269–270	147	
α-Yohimbic acid	287	49.6	
β-Yohimbic acid	256	125.6	
γ-Yohimbic acid	252	89.5	
Quebrachoic acid	269	138.8	
Corynanthic acid	256	−58	

Eight isomeric yohimbines are known; when saponified with alcoholic KOH, they yield eight isomeric carboxylic acids, $C_{20}H_{24}N_2O_3$, of which several occur naturally beside the alkaloids. Besides the two oxygen atoms in the carboxyl group, the yohimbines contain a hydroxyl oxygen atom. The close relationship of these alkaloids is shown by the decarboxylation of the acids from them to the same *yohimbol*, $C_{19}H_{24}N_2O$, m.p. 306° (dec.), $[\alpha]_D$ −100, except for alloyohimbic, α-yohimbic and corynanthic acid (alloyohimbic acid gives the *yohimbol*, m.p. 230°, $[\alpha]_D$ +144.6°). All the isomers are converted by dehydrogenation with selenium to the same optically inactive base ($(C_{18}H_{12}N_2)_2O$ (?), m.p. 211° (dec.) (*Hahn, Schuch*, Ber. **63**, 1638).

From a comparison of the differences in acidity and in pharmocological properties, the carboxyl groups of yohimbenic, isoyohimbic and yohimbic acids are probably in the 2-, 3-, and 4-positions of a pyridine ring (*Hahn, Brandenburg*, Ber. **59**, 2192). The assignment of the 2-position to the carboxyl group of yohimbenic acid is supported by the easy conversion of the methylbetaine of this acid to the methyl ester (*Hahn, Stenner*, Ber. **61**, 278).

Treatment of yohimbine with concentrated H_2SO_4 converts it to the unsaturated *apoyohimbine*, $C_{21}H_{24}O_2N_2$, m.p. 252°, which yields *desoxyyohimbine*, $C_{21}H_{26}O_2N_2$, m.p. 203°, on catalytic hydrogenation (*Barger, Field*, J. **123**, 1038).

The two N atoms in yohimbine are tertiary. While one is able to add methyl iodide, and is open to exhaustive methylation, the other, when acetylated, shows the *Tiffeneau* decomposition reaction, which is typical of tertiary benzylamines (*Tiffeneau, Führer*, Bull. [4] **15**, 162; *Tiffeneau*, Bull. [4] **17**, 67). This reaction was most closely investigated for isoyohimbine: by treatment with acetic anhydride the unsaturated *diacetyl derivative*, $C_{21}H_{24}N_2O_3(COCH_3)_2$, m.p. 185°, $[\alpha]_D$ −20.8°, is formed; on catalytic hydrogenation with Pd and H_2 this adds hydrogen to give the corresponding *dihydro derivative*, m.p. 177°. Alloyohimbine yields only one *monoacetyl compound*, m.p. 176° (dec.). The alkaloids can be regenerated from the acetyl compounds by saponification and methylation (*Hahn, Schuch*, Ber. **62**, 2953).

Of the basic ring structure of the yohimbine alkaloids, only fragments can be recognized. The oxidation with $KMnO_4$ gives N-*oxalylanthranilic acid*, m.p. 202–203° (dimethyl ester, m.p. 152°) (*Späth, Bretschneider*, Ber. **63**, 2997), and *hydroxycarbanil*, m.p. 137° (*Warnat*, Ber. **59**, 2388). Among the products of pyrolysis which have been isolated are the *base*, $C_{13}H_{12}N_2$, m.p. 230–232° (picrate, m.p. 258–260°), an *indole homologue*, m.p. 55° (picrate, m.p. 157°), and the *picrate of a base*, C_9H_7N, m.p. 216–218° (*Stedman*, Ber. **60**, 1009; *Warnat*, Ber. **60**, 1119; *Winterstein, Walter*, Helv. **10**, 577).

HELLEBORE (VERATRUM) ALKALOIDS occur together with veratric acid (3,4-dimethoxybenzoic acid) in the white hellebore, *Veratrum album*, and in the cevadilla, *V. sabadilla*. **Veratrine** or **cevadine**, $C_{32}H_{49}NO_9$, m.p. 202°, $[\alpha]_D$ +12.5° (alcohol), crystallizes from alcohol with two molecules of alcohol of crystallization; it dissolves in concentrated sulfuric acid with a yellow color which gradually becomes blue-red. It is split by alcoholic KOH into **cevine**, $C_{27}H_{43}NO_8 \cdot 3^1/_2\, H_2O$, m.p. 195–200°, and tiglic acid, $C_5H_8O_2$ (Vol. I, p. 346) (*Freund, Schwarz*, Ber. **32**, 800; *Macbeth, Robinson*, J. **121**, 1571). On distillation with soda lime, *l*-coniine is obtained (*Macbeth, Robinson*, J. **121**, 1571). Cevadine contains a free hydroxyl group, $C_{27}H_{41}NO_6(OH)(O \cdot COC_4H_7)$, while cevine has two hydroxyl groups, $C_{27}H_{41}NO_6(OH)_2$; the nitrogen atom is apparently joined with three other atoms (*Freund*, Ber. **37**, 1946). For suggestions concerning its constitution, see *Macbeth, Robinson*, J. **121**, 1571.

A series of subsidiary alkaloids have also been isolated: *veratridine*, *cevadilline*, and *sabadine*. Their homogeneity is not definitely established (*Hess, Mohr*, Ber. **52**, 1984).

ACONITUM ALKALOIDS. From the poisonous roots of numerous Japanese varieties of *Aconitum*, *Majima* has isolated several alkaloids. Almost all of these contain one molecule of acetic acid and one molecule of an aromatic acid in the form of esters; partial saponification with 15% H_2SO_4 removes the acetic acid, while the aromatic acid is eliminated under more energetic treatment (in a pressure tube or with alcoholic KOH). The resulting alkamines can be obtained in a crystalline condition only in the form of their acetyl derivatives. A summary of the physical data of the alkaloids of this group isolated up to the present time and the products of their hydrolysis is given in the following references: *Majima, Morio*, Ber. **57**, 1473; Ann. **476**, 203.

The thermal decomposition of the alkaloids yields new basic substances. *Aconitine*, $C_{37}H_{47}NO_{11}$, m.p. 202–203°, loses one molecule of acetic acid and forms *pyraconitine*, $C_{32}H_{43}NO_9$, m.p. 271–272°; *hypaconitine*, $C_{33}H_{45}NO_{10}$, m.p. 198.5°, gives the analogous *pyrohypaconitine*, $C_{31}H_{41}NO_8$, m.p. 119–120°.

The oxidation of aconitine, $C_{34}H_{47}NO_{11}$, and of *mesaconitine*, $C_{33}H_{45}NO_{11}$, m.p. 208–209°, with permanganate leads to the same decomposition product, **oxonitine**, $C_{32}H_{43}NO_{12}$, m.p. 282°, $[\alpha]_D$ −41° (*Spath, Galinovsky*, Ber. **63**, 2994).

ERGOT ALKALOIDS. From ergot, which is used medicinally to contract blood vessels, the following alkaloids have been isolated; their molecular formula is not known with certainty in every case [*Tanret*, Bull. [4] **31**, 444; *Forst*, Arch.exptl.Path.Pharm. **114** (1926), 125; *Smith, Timmis*, J. **1930**, 1390].

Ergotoxine, $C_{35}H_{41}O_6N_5$, m.p. 190–200°.
Ergotinine, $C_{35}H_{39}O_5N_5$, m.p. 239°.
Ergotamine, $C_{33}H_{35}O_5N_5$, m.p. 213–214°.
Ergotaminine, $C_{33}H_{35}O_5N_5$, m.p. 252°.

PART II
ORGANIC FREE RADICALS

ORGANIC FREE RADICALS

BY LUDWIG ANSCHÜTZ

Note on method of writing formulas and quoting literature. Greater clarity is obtained by writing the formulas of free radicals with straight lines for the free valences instead of a series of points, or broken lines. In order to save space, only the senior author of a piece of research is given in a reference. This also makes it easier to find later contributions from the same school.

GENERAL PART

LITERATURE: *J. Schmidlin*, "Das Triphenylmethyl," Vol. VI of "Chemie in Einzeldarstellungen," Enke, Stuttgart, 1914.

R. Pummerer, "Organische Chemie," Vol. III of the "Naturwissenschaftlichen" series of "Wissenschaftliche Forschungsberichte," section on radicals (pp. 11–34), Steinkopff, Dresden and Leipzig, 1923.

P. Walden, "Chemie der freien Radikale," Hirzel, Leipzig, 1924; "Aus der Lebensgeschichte einiger organischer Radikale," Z.angew.Chem. **39,** 601 (1926).

F. Henrich, "Neuere Untersuchungen über organische Radikale aus den Jahren 1922 bis 1928," Z.angew.Chem. **41,** 1214, 1239 (1928).

K. Ziegler, "Probleme und Ergebnisse der neueren Erforschung der freien Radikale," Z.angew.Chem. **43,** 915 (1930).

W. Hückel, "Theoretische Grundlagen der organischen Chemie," section on free radicals, 2nd ed., Vol. I, pp. 111–133, Akadem. Verlagsgesellschaft, Leipzig, 1934; "A General Discussion on Free Radicals," Trans.Faraday Soc. **30,** 3–248 (1934).

F. O. Rice and *K. K. Rice*, "The Aliphatic Free Radicals," Oxford Univ. Press, 1935 (204 pp.).

Introduction. *H. Wieland* (Ber. **48,** 1098) defined radicals as "free unsaturated complexes of an atomic character and of abnormal valencies." Normal ions were excluded by *Wieland* by the addition of the words "that radicals, like atoms, have no electric charge." *P. Walden* (Chem. der fr. Rad., p. 43) extended *Wieland's* definition to cover a series of electrically charged groups of atoms. *W. Hückel* in his "Theoretische Grundlagen," 2nd ed., Vol. I, p. 111, gives the following conception of a free radical: "In the free radicals, the valency of an element is one lower than corresponds to its position in the periodic table." According to this idea, not only neutral compounds but also ions—both anions and cations—are included as free radicals, provided they contain an element with a valency lower by one unit than the ordinary." *W. Schlenk* (Inst.int.Chim.Solvay Conseil Chim. **4,** 503) pointed out that the univalent free radicals can be recognized by their odd number of valency electrons. They can be defined on the basis of the quantum theory as compounds, of which the electron system has an unsaturated spin moment (see *R. Mecke*, Trans. Faraday Soc. **30,** 200). Organic radicals are all radicals containing carbon. Those radicals containing trivalent carbon are of special importance in organic chemistry.

Important historical data. In 1787, *Lavoisier* introduced the term "radical," the meaning of which has undergone many changes since that time. The concept of radicals served as the starting point for the development of a theoretical system (old and new radical theory). The most important experimental confirmation of this idea came from the preparation of cyanogen by *Gay-Lussac* (1815), the work on the radical of benzoic acid by *Liebig* and *Wöhler* (1832), the preparation of cacodyl by *Bunsen* (1841), and the work of *Kolbe* and *Frankland* on the preparation of hydrocarbons with an assumed radical nature (1849 and 1850). In 1900 the first compound which was actually a free radical was prepared by *Gomberg,* who obtained triphenylmethyl, the first radical containing trivalent carbon, by the action of zinc on a benzene solution of triphenylmethyl chloride. He showed, however, that the new compound was not pure, but existed in equilibrium with hexaphenylethane. The work on this particularly difficult problem was chiefly carried out by *J. Schmidlin* (1908), *H. Wieland* (1909), *W. Schlenk* (1910), and *J. Piccard* (1911). *Schmidlin* showed that triphenylmethyl existed in a colored (monomeric) and a colorless (dimeric) form. *Wieland* demonstrated the dissociation of hexaphenylethane by molecular weight determinations in molten naphthalene. *Schlenk* replaced the phenyl groups of triphenylmethyl one-by-one with biphenylyl radicals, and finally obtained tribiphenylylmethyl, which is monomolecular in solution. He thus obtained the first pure free radical in the form of green crystals. *Piccard* made the interesting observation that the color of solutions of triphenylmethyl deepened on dilution, in contradiction to *Beer's* law. This was due to increasing dissociation of the hexaphenylethane. *W. Schlenk* and his school (1911–1913), recognized a new class of free radicals with trivalent carbon in the metallic ketyls, which had first been obtained by *E. Beckmann* and *T. Paul* in 1891. In more recent times *F. Paneth* has developed a method for the detection of the exceedingly short-lived radicals, methyl and ethyl (1929, 1931). *H. Wieland* obtained the first organic radical with di- or tetra-valent nitrogen (1911, 1914). *E. Weitz* discovered the "aminium" salts, with a positively charged radical-ion, which, according to its formula, contains tetravalent nitrogen (1926). The discovery of compounds with univalent oxygen is chiefly due to *R. Pummerer* and *S. Goldschmidt* (1913, 1922). Many other elements in organic compounds are now known with valencies one less than the usual.

Theoretical treatment of formation of radicals. The theoretical conclusion to which the discovery of free radicals has led is "the clear recognition of the divisibility of valency" (*W. Schlenk,* Ber. **55,** 2285). The inequality of different links follows. In this way, *Thiele* (Ann. **319,** 134), and later *Werner* (Ber. **39,** 1282), explained the existence of the free triarylmethyls on the particularly great valency demands of the three aryl groups. Later, however, it became clear that this conception did not lead to a useful theory of general application (for the complete overthrow of these ideas, see *C. K. Ingold,* Proc.Leeds Phil.Lit.Soc. **1,** 421). *K. Ziegler* and his co-workers have made extensive studies on the question of what factors favor the decomposition of the substituted ethanes into radicals (Ann. **479,** **111,** and earlier papers). It has been shown that the introduction of unsaturated substituents (which, according to the *Thiele-Werner* theory, make particularly great valency demands) makes a substituted ethane dissociate six times more readily than a saturated substituent (Ann. **434,** 34). Other considerations are also important, *e.g.,* the space occupied (Ann. **473,** 194), and the electrochemical character (Ann. **479,** 111) of the substituents. The examination of this latter question for the hydrazyls of the type $Ar_2N \cdot N(Ac) \cdot$ is due to *Goldschmidt* (Ann. **473,** 137). The effect of ring strain on the formation of radicals has been investigated experimentally by *Wittig* and his co-workers (Ann. **505,** 17, and earlier papers). A satisfactory general explanation of radical formation is still, however, lacking, in spite of the many experimental investigations that have been made. Instead, the difficulty of fitting into one system the ever-growing body of facts has increased. *Wieland* and his co-workers (Ann. **381,** 217, and earlier papers), for example, reach the surprising conclusion that the effect of substituents on the tendency to dissociation of the hexaarylethanes cannot be applied to that of the tetraarylhydrazines. *Schlenk* and *Mark* (Ber. **55,** 2285) have found that pentaphenylethyl is a substance with an unusually small tendency towards association, in contradiction with the *Thiele-Werner* principle. These examples could easily be increased (*cf. Goldschmidt,* Ber. **55,** 633; Ann. **437,** 208). It is therefore understandable that in more recent times various authors have applied exact physicochemical methods in order to obtain a deeper insight into the question of radicals and their formation (see *Ziegler,* Z.angew.Chem. **43,** 915).

The physicochemical work on the problems of the chemistry of radicals starts with molecular weight determinations by the osmotic methods by *Gomberg* (Ber. **34,** 2731) and carried on by *Schlenk* (Ann. **372,** 5). By this means the important result was obtained that tribiphenylylmethyl is completely monomolecular in solution, proving the existence of trivalent carbon. The later extensive determinations of molecular weights by *Gomberg* and his co-workers using numerous triarylmethyls were used by *Walden* (Chem.der fr.Rad., p. 286) to calculate the dissociation constants of the dissolved hydrocarbons (see *Schönberg,* Ber. **66,** 1938). In sufficiently dilute solution the *Ostwald* dilution law (originally worked out for weak electrolytes) applies. The dissociation constant, k, can be calculated from the degree of dissociation, α, and the dilution, v, according to the following equation:

$$k = \frac{\alpha^2}{(1 - \alpha)v}$$

Temperature and the nature of the solvent used also influence the degree of dissociation (see *Hückel,* Grundlagen, Vol. I, p. 129). *Goldschmidt* and his co-workers have investigated cases of dissociation into radicals, which involve the formation of compounds with divalent nitrogen (Ann. **473,** 137, and earlier papers), and monovalent oxygen (Ann. **445,** 123, and earlier papers). The dissociation constants of these compounds in numerous solvents were determined by titration of the dissociated portion (Ann. **437,** 200; **438,** 208; **473,** 141; for further details, see diarylacylhydrazyls and phenanthroxyls). The heat of dissociation can be obtained from the variation of the dissociation constant with temperature (Ann. **473,** 143). Other methods of obtaining the dissociation constant use the determination of the intensity of color of the solution of the radical at increasing dilution (determination of the molecular extinction coefficient) (*Goldschmidt,* Ann. **473,** 144). In this way the equilibrium constant and (from its variation with temperature) the heat of dissociation of hexaphenylethane have been determined (*Ziegler,* Ann. **473,** 163; see *Schönberg,* Ber. **66,** 1938). They obey the *Arrhenius* equation:

$$-D = R\frac{T_1T_2}{T_2 - T_1}\log\frac{K_2}{K_1}$$

where K_1 and K_2 are the equilibrium constants at the absolute temperatures T_1 and T_2. Since this equation is deduced for the gaseous state, and the determinations are made in solution, it is necessary to find out what effect the solvent has on the results. In contradiction to *Goldschmidt* (Ann. **473,** 147), *Ziegler* (Ann. **473,** 180) found that the heat of dissociation, at least of hexaphenylethane, is constant, independent of the solvent. Of greater interest than the determinations of heat of dissociation are the determinations of the velocity of spontaneous decomposition of the substituted ethanes at various temperatures that have been carried out by various workers in more recent times (*Conant,* Am. **51,** 1925; *Branch,* Am. **52,** 255; *Ziegler,* Ann. **479,** 277; **504,** 131). From the variation with temperature of the decomposition constant it is possible (with the aid of the *Arrhenius* equation) to obtain the heat of activation of the compound. In this way, an exact determination of the amount of energy that has to be imparted to a substance R—R in order to break it down, may be made, and hence the strength of the bond linking the two radicals together in the dimer is obtained. A comparison of the heat of dissociation and the heat of activation for one particular compound is of considerable theoretical interest, as *Ziegler* (Ann. **504,** 147) has shown on the basis of extensive series of experiments with hexaphenylethane. In the case of hexaphenylethane, if it were shown that the heat of dissociation were equal to the heat of activation, this would mean that triphenylmethyl was the first radical-like fission product of the dimer. On the other hand, if the heat of dissociation is less than the heat of activation, as *Ziegler* found, it must be concluded that triphenylmethyl is a more stable product than the initially formed radical, whatever that may be. This stabilization could be effected intramolecularly by distortion of valency bonds, or extramolecularly through the solvent. In connection with these results it is interesting to take into account some of the more recent work, in which it has been shown that in liquid ammonia solutions of phenols and aromatic acids, active radicals (excited molecules in the sense of modern physics) exist, which differ from the earlier known radicals containing monovalent oxygen, obtained by dehydrogenation of phenols, in their enhanced reactivity (*Goldschmidt*, Ber. **64,** 1744; see also *Ziegler*, Ann. **504,** 162).

Finally, the very interesting observation that the solid, colorless forms of the hexa-substituted ethanes are dissociated by the application of very high pressure must be mentioned. This means that two single radical molecules occupy a smaller volume than one molecule of the dimer (*Löwenbein*, Ber. **60,** 1855; see also *Ziegler*, Ann. **473,** 194). For "valency tautomerism," where the radicals are in equilibrium with normal isomers with the correct valencies, or with isomeric radicals, see *Pummerer*, Ber. **52,** 1410; *Wieland*, Ber. **53,** 1318; *Schönberg*, Ber. **64,** 2323; *Clar*, Ber. **66,** 202 (see, however, *Conrad-Billroth*, Ber. **66,** 639); *Wittig*, Ann. **483,** 144; *Ziegler*, Ann. **504,** 189. For "polycentricity" as the origin of the lack of tendency of association of the valency tautomeric free radicals, see *Löwenbein*, Ann. **487,** 97. For stereochemistry of asymmetric free triarylmethyls ($\cdot CAr'Ar''Ar'''$) see *Gomberg*, Ber. **37,** 2036; *Schmidlin*, Ber. **45,** 3183; *Karagunis*, N. **21,** 607; *Wallis*, Am. **53,** 812; **55,** 3838; **56,** 491. For "ultradissociation" (which has not yet been strictly proved), of the free triarylmethyls and other open questions connected with the chemistry of free radicals (especially discussing numerous cases where the experimentally determined molecular weight of an organic compound was too low), see *Walden*, Chem.der fr.Rad., pp. 299 *ff.* For potential determinations with the triarylmethyls, see *Conant*, Am. **47,** 1959; **55,** 3752. For electron affinity of free radicals, see *Bent*, Am. **54,** 3250. For *Hückel's* application of quantum theory to free radicals, see Z.Physik, **83,** 632; Ann. **504,** 149; *Pauling*, J.Chem.Phys. **1,** 362.

Investigation of the behavior of radicals. For the behavior of carbonium salts, see *Hantzsch*, Ber. **54,** 2573-2633. The comparison of the absorption spectra of triphenylmethyl as a cation, as an anion, and as a free radical, is specially dealt with. For conductometric experiments (usually with dissolved triarylmethyl halides), see *Walden*, Ber. **35,** 2018; Z.physikal.Chem. **43,** 385; *Gomberg*, Am. **45,** 190, and earlier papers; *Hofmann*, Ber. **43,** 186; *Schlenk*, Ann. **372,** 11; Ber. **47,** 1678; **49,** 606; **50,** 278; *Hantzsch*, Ber. **43,** 336; **54,** 2601; *Straus*, J.pr. **103,** 1-68; *etc.* For valency considerations and stability of organic radicals, see *Auwers*, Ber. **57,** 1051; *Braun*, Ber. **63,** 2407, and earlier papers; *McKenzie*, J.Soc.Chem.Ind.London **50,** 926; *Meerwein*, Ann. **419,** 121; *Skraup*, Ber. **55,** 1073, *etc.* For methods of determining the relative electronegative character of organic radicals, see *Kharasch*, Am. **54,** 674; *Migita*, Bull.Chem.Soc.Japan **8,** 27. The behavior of radicals of high affinity content and negative character is discussed by *Urbain*, J.chim.phys. **29,** 325; the distribution of electronic linkages by *Craig*, Am. **53,** 4367, and *Starr*, Am. **54,** 3971; and electron affinity of radicals by *Zaki*, J. **1932,** 1184.

Occurrence of free radicals in chemical reactions. *Walden*, Chem.der fr.Rad., p. 278; *Hückel*, Grundlagen, Vol. I, p. 110; *Wieland*, Ann. **513,** 93, and earlier papers; *Hein*, Z. Elektrochem. **28,** 469; *Goldschmidt*, Ber. **55,** 3216; *Haber*, Ber. **64,** 2844; *Schlenk*, Inst.int.Chim. Solvay, Conseil Chim. **4,** 503; *Burawoy*, Z.physikal.

Chem. **A164,** 1; *Rice*, Am. **55,** 3035; *Gilman*, Am. **55,** 2893; *Ziegler*, Ann. **504,** 162; *Wittig*, Ann. **513,** 26; *etc.*

Technique. The fact that free radicals are usually very readily attacked by oxygen or moisture requires that they should be investigated in an atmosphere of a dry indifferent gas, or in a vacuum. This is particularly true of the compounds of trivalent carbon, and the method of dealing with them will be described in some detail.

Detection of free radicals: *I. Physical methods.*—(*a*) Osmotic methods of determining molecular weights (lowering of freezing point and elevation of boiling point); (*b*) colorimetric methods (inaccuracy of *Beer's* law); (*c*) spectroscopic methods; free radicals in solution usually give characteristic absorption bands, and in the gaseous state band spectra with a characteristic fine structure. Their existence at high temperatures can be detected by their emission spectra. The mass spectrograph can also be used (see *Mecke*, Trans. Faraday Soc. **30,** 200); (*d*) electrolysis (particularly valuable for the cathodic separation of ammonium radicals); (*e*) detection of paramagnetism as the consequence of unpaired electrons; *Lewis*, Proc. Nat.Acad.Sci. **11,** 456; see also *Cambi*, Gazz. **63,** 579; *Katz*, Z.Physik **87,** 238; *Galavics*, Helv.physica Acta **6,** 555; *Sugden*, Trans.Faraday Soc. **30,** 18; *Kuhn*, Ber. **67,** 362; *Müller*, Ann. **517,** 134.

II. Chemical methods.—Their tendency to disproportionation is characteristic of radicals containing hydrogen (*Wieland's* rule, Ann. **401,** 234). The powers of addition, particularly of other radicals, are also important. Other reactions indicate even more clearly the tendency to become saturated on the part of a radical. The compounds thus formed often give some proof of the existence of very short-lived radicals (*e.g.*, methyl, see *Paneth*, Ber. **62,** 1335).

Limitation of subject. There are a considerable number of substances the radical nature of which is disputed. To this class belong particularly those radicals with a semiquinoid constitution which have been regarded as such by *Michaelis* on the basis of potentiometric observations (see N. **19,** 461; Am. **53,** 1953; J.Biol.Chem. **96,** 703; Am. **55,** 1481; *Hantzsch*, Ber. **49,** 519; *Piccard*, Ber. **59,** 1438). Wurster's red is a compound of this sort that has been widely studied by this and other methods. This compound, and many others of a similar kind were given only a meriquinoid structure (*Willstätter*, Ber. **41,** 1458). Later these compounds were explained in other ways (*Weitz*, Ber. **59,** 432; Z.Elektrochem. **34,** 538; *Dilthey*, J.pr. **118,** 321, *etc.*). The highly colored intermediate substances obtained by the reduction of certain dyes (such as pyocyanine, rosindulin GG, lactoflavin or vitamin B_2) are also regarded as radicals (*Kuhn*, Ber. **67,** 361). It does not appear advisable to treat all these compounds among the radicals, as it would mean taking them away from more important relationships. The arrangement of the substances dealt with is therefore not to be regarded as dictated by constitutional problems. Certain compounds of undoubted radical nature are only dealt with briefly here, and more fully elsewhere. For instance, the lead tetraaryls have been included in the section on the other aromatic compounds of lead. In general, the work is arranged so that the organogenic elements, carbon, nitrogen, and oxygen, are used as a basis. It has also been considered convenient to follow these three elements with those radical-forming elements which occur near them in the periodic system. Thus the elements in the vertical series of Groups IV, V, and VI in the periodic system are dealt with in order, in so far as they enter into the formation of organic radicals. Two other elements come into radical formation; they are in the third vertical series. The following, then, is the arrangement: **IV**—C, Si, Sn, Pb; **V**—N, P, As, Sb; **VI**—O, S, Cr; **III**—B, Al. If radicals of one particular element are known in different valency stages, the types with the higher valency are considered.

1. SPECIAL PART

I. RADICALS WITH TRIVALENT CARBON. CARBYLS

The most important compounds with trivalent carbon are the hydrocarbon radicals. It has been shown that a loading with aromatic or other unsaturated groups is necessary in order to hinder the practically complete dimerization of these radicals. The triarylmethyls are the most interesting members of this class, both on historic and theoretical grounds. These, together with the closely related trisubstituted methyls will be considered first. These compounds may be referred to shortly as "trityls"—an extension of the abbreviation "trityl" recommended in *Beilstein's* "Handbuch" (4th ed., Vol. V, 9) for triphenylmethyl.

(a) Trityls (Triarylmethyls and Analogous Compounds)

As mentioned above, the triarylmethyls exist in equilibrium with the hexaarylethanes (*Wieland*, Ber. **42**, 3028). Whether this equilibrium is displaced to the right or to the left depends chiefly on the nature of the attached groups. In the methods of formation of the trityls dealt with below, this equilibrium will not be further mentioned.

METHODS OF FORMATION. *I. Breaking of the bond between the trityl radical and halogen* (or perchlorate radical).

1. The classical method of *Gomberg* (Ber. **33**, 3150) for the preparation of the triarylmethyls consists in the action of metals (silver, mercury, zinc) on the triarylmethyl chloride in benzene solution in an atmosphere of carbon dioxide:

$$Ar_3C—Cl + Ag = Ar_3C— + AgCl$$

Copper, magnesium, and nickel may also be used. The action of magnesium takes place in two phases (see *Schmidlin*, "Triphenylmethyl," p. 38). Molecular silver is particularly effective (*Gomberg*, Ber. **39**, 3286), and *Schlenk* has used molecular copper (Ber. **43**, 1754) or copper bronze (Ann. **372**, 2; Ber. **44**, 1172). Nickel carbonyl acts like nickel. The metal takes part in the reaction after splitting off carbon monoxide (*Schlenk*, Ber. **44**, 1176).

2. **Phenylmagnesium iodide** may be used to remove the halogen from triphenylmethyl chloride (*Schmidlin*, Ber. **43,** 1141):

$$2\,(C_6H_5)_3C—Cl + 2\,C_6H_5MgI = 2\,(C_6H_5)_3C— + C_6H_5—C_6H_5 + 2\,MgClI$$

The analogous method of acting upon trityl perchlorates with phenylmagnesium bromide is of considerable preparative use (*Ziegler,* Ann. **434,** 34).

3. **Sodium diethylphosphite** removes the halogen smoothly from triphenylmethyl bromide (*Arbusov,* Ber. **62,** 1871).

4. *Conant* (Am. **45,** 2466) found that vanadous chloride and chromous chloride would remove the acid radical from trityl chlorides and other "onium" salts (*Conant,* Am. **47,** 572; *Ziegler,* Ann. **448,** 253):

$$R—Cl + VCl_2 = R— + VCl_3$$
$$R—Ac + CrCl_2 = R— + CrCl_2Ac$$

5. Triphenylmethyl chloride reacts with **sodio-triphenylmethyl** forming triphenylmethyl. This shows that not only the halogen but also the sodium is loosely held by the hydrocarbon radical (*Schlenk,* Ber. **47,** 1667).

$$(C_6H_5)_3C—Cl + Na—C(C_6H_5)_3 = NaCl + 2\,(C_6H_5)_3C$$

6. An analogous reaction takes place between triarylmethyl chlorides and triarylmethanes in sunlight (*Schlenk,* Ber. **43,** 3544):

$$Ar_3C—Cl + H—CAr_3 = HCl + 2\,ArC_3$$

The chemical methods of removing halogen from the trityl halides are followed by some methods of theoretical rather than practical interest, which depend on the spontaneous decomposition of the halides or their decomposition by physical methods:

7. The halogen in triphenylmethyl iodide is so loosely held by the hydrocarbon radical that the compound breaks down to the extent of $^1/_5$ even at ordinary temperatures (*Gomberg,* Ber. **35,** 1826).

$$(C_6H_5)_3C—I = (C_6H_5)_3C— + I$$

8. The halogen can be removed from triphenylmethyl chloride by means of cathode rays (*Schlenk,* Ann. **372,** 14).

9. Trityl halides, dissolved in liquid sulfur dioxide, can be electrolyzed, when $(C_6H_5)_3C—$ separates at the cathode. Complex ions must play some part (triarylmethyl halides form addition compounds with sulfur dioxide, *Schlenk,* Ann. **372,** 9).

II. Breaking of the bond between the trityl radical and sodium (or potassium; method *5* may be included here also).

10. Sodio-triphenylmethyl can be decomposed into the radical and sodium peroxide by careful shaking with air. The tetramethylammonium compound of the trityl radical behaves similarly:

$$2\,(C_6H_5)_3C—Na + O_2 = 2\,(C_6H_5)_3C— + Na_2O_2$$

11. The metal can also be removed by the action of aromatic ketones. Metallic ketyls are formed (see later):

$$(C_6H_5)_3C—Na + O{=}CAr_2 = (C_6H_5)_3C— + NaO—CAr_2$$

12. An almost ideal method of removing the metal is by means of **tetramethylethylene bromide** (*Ziegler*, Ann. **437,** 232):

$$2\,Ar_2RC{-}K + (CH_3)_2CBr{-}CBr(CH_3)_2 = (Ar_2RC{-})_2 + (CH_3)_2C{=}C(CH_3)_2 + 2\,KBr$$

An important reaction by which the starting material for the above reaction can be obtained depends on the power of tertiary ethers, which contain at least one aromatic group attached to the central carbon atom, to break down when treated with potassium:

$$Ar_2RC{-}O{-}CH_3 + 2\,K = Ar_2RC{-}K + K{-}O{-}CH_3$$

(*Ziegler*, Ann. **437,** 227, 241; see also Ber. **56,** 1740, 2453).

13. **Tritylmagnesium chloride** enters into similar reactions to the trityl alkali metals (see *Schmidlin* "Triphenylmethyl," p. 40).

III. *Breaking the bond between trityl radical and nitrogen,* which is possible under certain circumstances (*Wieland*).

14. The dissociation of trityldiphenylamine in boiling xylene is interesting from the theoretical point of view (*Wieland,* Ann. **381,** 215):

$$(C_6H_5)_3C{-}N(C_6H_5)_2 = (C_6H_5)_3C{-} + {-}N(C_6H_5)_2$$

15. The decomposition of **azo-triphenylmethane,** which occurs even at 0°, is of some preparative importance. The azo-compound is readily obtained by oxidation of the corresponding hydrazo-compound (*Wieland,* Ber. **42,** 3021):

$$(C_6H_5)_3C{-}N{=}N{-}C(C_6H_5)_3 = 2\,(C_6H_5)_3C{-} + N_2$$

16. The study of the analogous fission of **triarylmethaneazobenzene** and similar compounds, $Ar_3C{-}N{=}N{-}Ar$, has given valuable conclusions on the occurrence of free aryls in chemical reactions, and led to the preparation of the radical of the basic triphenylmethane dyes (*Wieland,* Ber. **55,** 1816).

IV. *Breaking the bond between trityl radical and oxygen.* This occurs in trityl ethers and is only of theoretical interest. See also *12* above.

17. **Hydroquinone-*bis*-trityl ether** decomposes on heating into quinone and two trityl molecules (*Schmidlin,* Ber. **43,** 1302).

V. *Breaking the bond between trityl radical and sulfur* (*Blicke,* Am. **45,** 544, 1965).

18. **N-Pentamethylene-S-trityldithiourethan,** $C_5H_{10}N{\cdot}C({:}S)S{\cdot}CAr_3$, breaks down in solution even at ordinary temperature forming the free trityl.

19. **Trityldisulfide** behaves similarly.

VI. *Breaking the C—C bond between two trityl radicals.* The breaking of this linking is implied in all the above methods for obtaining trityls. If this does not take place, the practically pure dimer is obtained (see, for example, method *12*).

20. In many cases polyarylethanes, which are not dissociated at all at ordinary temperature, may be dissociated on heating (*Schlenk,* Ber. **43,** 3542):

$$2\,Ar_3C{-}CHAr_2 \xrightarrow{150^\circ} 2\,Ar_3C{-} + ({-}CHAr_2)_2$$

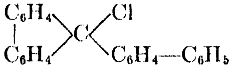
The decomposition of asymmetric polyarylethanes is of special interest, since each of the two fission products can dimerize, and three equilibria exist. The most important dissociation of this kind occurs with octaphenylpropane. It is almost complete at ordinary temperatures. Its study led to the discovery of pentaphenylethyl by *Schlenk* and *Mark* (Ber. **55**, 2285):

$$Ar_3C—CAr_2—CAr_3 = Ar_3C— + —CAr_2—CAr_3$$

METHOD. In the preparation of the triarylmethyls it is essential to exclude air, as the radicals are very readily attacked by it. Air is replaced by an indifferent gas. Carbon dioxide, hydrogen, and nitrogen have been used for this purpose. Carbon dioxide cannot, however, always be used, as it sometimes reacts with the materials from which the radicals are prepared, *e.g.* Ar_3CNa. For the same reason it is often necessary to exclude all moisture, though the triarylmethyls themselves are not attacked by water (*Schlenk*, Ber. **44**, 1174). The rapid diffusion of hydrogen makes its use unsuitable in many types of apparatus. In general, therefore, the triarylmethyls are prepared in a current of nitrogen. For details of the apparatus for obtaining and working with the triarylmethyls, see *Gomberg*, Ber. **37**, 1629, 2034, 2044; Am. **39**, 1652; *Schmidlin*, Ber. **41**, 423; **45**, 3176, 3186, 3191; *Schlenk*, Ann. **372**, 16; Ber. **46**, 2843; *Houben-Weyl*, Method. der org. Chem., 2nd ed., IV, 959 *ff*.; *Ziegler*, Ann. **434**, 64; **445**, 281; **473**, 182; **479**, 105, 302; **504**, 152. Some of these methods are reviewed in *Walden*, Chem. der fr. Rad., pp. 58–63, 87, 119, 122. *Schlenk*, Ber. **46**, 2843, has developed a very simple and elegant method of working with sensitive radicals, in his work on the metallic ketyls (*q.v.*).

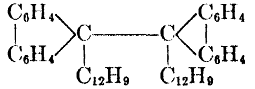
PROPERTIES. The essential properties of the triarylmethyls are governed by their tendency towards association. This depends on the type of substituents (*Schlenk*). On the one hand it can be entirely lacking, as in tribiphenylylmethyl, $(p\text{-}C_6H_5—C_6H_4—)_3C—$, of which the dimer is unknown (Ann. **372,** 1). On the other hand, it can be so strong that only the dimer is known.

This is the case with the hydrocarbon obtained from biphenylene-*p*-biphenylylmethyl chloride:



$$\begin{array}{l} C_6H_4 \\ | \\ C_6H_4 \end{array} > C < \begin{array}{l} Cl \\ \\ C_6H_4—C_6H_5 \end{array}$$

which is only known as the completely undissociated dibiphenylenedibiphenylylethane (*Schlenk*, Ann. **372,** 21):



$$\begin{array}{l} C_6H_4 \\ | \\ C_6H_4 \end{array} > \underset{C_{12}H_9}{\underset{|}{C}} ——— \underset{C_{12}H_9}{\underset{|}{C}} < \begin{array}{l} C_6H_4 \\ | \\ C_6H_4 \end{array}$$

The triarylmethyls are highly colored; their dimers are colorless. The majority of the triarylmethyls show a tendency toward association between the two extremes. In the solid form they are colorless and therefore dimeric (*Schmidlin*, Ber. **41,** 2473; *Schlenk*, Ber. **43,** 1757). In their colored solutions there is an equilibrium between the ethane form and the radical. The color of these solutions deepens on dilution, contrary to *Beer's* law. This is due to displacement of the equilibrium toward the monomeric form (*Piccard*, Ann. **381,** 347). Increase of temperature gives the same effect, and cooling reverses it (thermochromism). The trityls have characteristic band spectra

(*Meyer, Wieland,* Ber. **44,** 2557). Their solutions in benzene, acetylene tetrachloride, or nitrobenzene do not conduct electricity, but their solutions in liquid sulfur dioxide do (*Walden,* Z.physikal.Chem. **43,** 443; *Gomberg,* Ber. **37,** 2045). This may be due to the formation of complex ions. For an exhaustive account of the colorimetric, spectroscopic, and conductometric work on the triarylmethyls, see *Walden,* Chem.der fr.Rad., pp. 190, 182, 154.

CHEMICAL PROPERTIES. The outstanding chemical property of the triarylmethyls is their unsaturation. The following reactions are important:

1. **Oxygen** reacts very rapidly with triarylmethyls forming the colorless *bis*-triarylmethyl peroxides, which are difficultly soluble in the usual organic solvents (*Gomberg,* Ber. **33,** 3154):

$$2\,Ar_3C\text{—} + O_2 = Ar_3C\text{—}O\text{—}O\text{—}CAr_3$$

On this reaction and the equilibrium between triphenylmethyl and hexaphenylethane, depends the historically important "*Schmidlin* experiment":

> "Completely pure, colorless triphenylchloromethane is shaken with half a test-tube full of benzene and some zinc dust, the mouth of the tube being closed with the thumb. The yellow solution is filtered into a large, wide, test-tube. The filtered yellow solution becomes momentarily decolorized on shaking, but on standing becomes rapidly colored again. The color can be 'shaken away' many times."

For the mechanism of the oxidation of the triarylmethyls, in which the primary peroxidic radical with monovalent oxygen, $Ar_3C\text{—}O\text{—}O\text{—}$, is formed, and is the carrier of a reaction chain, see *Ziegler,* Ann. **504,** 162, 182. Details are also given of the stoichiometric oxidation in the presence of pyrogallol (method of estimating the dissociation constant of hexaarylethanes).

2. **Quinone** reacts with triphenylmethyl in the same way as oxygen. Two molecules of the radical add on (*Schmidlin,* Ber. **43,** 1300). This is the reverse of method of formation *17.*

$$Ar_3C\text{—} + O{=}C_6H_4{=}O + \text{—}CAr_3 = Ar_3C\text{—}O\text{—}C_6H_4\text{—}O\text{—}CAr_3$$

2a. **Isoprene** and similar substances add on two molecules of triarylmethyl in the same way, at the ends of the conjugated system (*Conant,* Am. **55,** 3475).

3. **Oxidizing agents** (chromic acid, permanganate) convert triphenylmethyl into triphenylmethanol (*Schlenk,* Ann. **394,** 182).

4. **Halogens** readily add on to triarylmethyls, though by the direct action of chlorine and bromine at −10°, substitution also occurs (*Gomberg,* Ber. **33,** 3158). The addition of iodine, which can be followed volumetrically, is not quantitative (see method of formation *7* and *Gomberg,* Am. **45,** 190; Ann. **479,** 292). The reaction goes to completion if quinoline is added. The quinoline removes the trityl iodide as it is formed, and in this case the reaction can be used for the determination of the concentration of a solution of the radical (*Ziegler,* Ann. **504,** 149). In contrast to iodine, bromine reacts with both triphenylmethyl and hexaphenylethane, of which the central bond is readily broken (*Ziegler,* Ann. **479,** 299).

5. **Hydrogen** reacts with triphenylmethyl only with difficulty, resembling in this respect the metals. Energetic hydrogenation, however, leads, as would be expected, to triphenylmethane (*Gomberg*, Ber. **36,** 381; *Schlenk*, Ber. **44,** 1174; *Schmidlin*, Ber. **45,** 3190; *Wieland*, Ann. **401,** 240).

6. **Sodium** and (more readily) potassium, react with the triarylmethyls with formation of highly colored addition products (*Schlenk*, Ber. **47,** 1664):

$$Ar_3C— + Na = Ar_3C—Na$$

The alkali metals are used in powder form, being obtained by shaking with hot liquids, *e.g.*, xylene (Na, m.p. 97.8°) and benzene (K, m.p. 62.5°).

Triphenylmethyl only reacts with difficulty according to this equation, being converted largely into *p*-**benzhydryltetraphenylmethane**. Brick-red triphenylmethyl sodium can, however, be prepared by the use of sodium amalgam and following a special method, without difficulty.

For the alkali metals as a reagent for weak valences in organic compounds see *Ziegler*, Ber. **56,** 1740. It is there mentioned that potassium will readily break down 1,1,2,2-tetraphenylethane, which is undecomposed at 380°.

In a similar manner to the above mentioned elements, radicals will also add on to the triarylmethyls:

7. **Nitric oxide** forms triphenylnitrosomethane with triphenylmethyl, but the substance is very unstable and cannot be isolated (*Schlenk*, Ber. **44,** 1170). For the determination of the dissociation constant of dissolved hexaarylethanes with the aid of this reaction (in the presence of aniline), see *Ziegler*, Ann. **504,** 137.

8. **Nitrogen dioxide** (or **tetroxide**) converts triphenylmethyl into (a little) triphenylnitromethane, and (much) triphenylmethyl nitrite. If the proportion of NO_2 molecules in the gas is increased by heating, the yield of triphenylnitromethane is increased (*Schlenk*, Ber. **44,** 1171):

$$(C_6H_5)_3C— + —NO_2 = (C_6H_5)_3C—NO_2$$

8a. For the formation of triphenylmethyl perchlorate from triarylmethyl and $(ClO_4)_x$, see *Gomberg*, Trans. Faraday Soc. **30,** 24.

9. **Nitrogen diaryls** (tetraarylhydrazines at the dissociation temperature) add on to triphenylmethyl (reverse of method of preparation *14*) to give trityldiarylamines (*Wieland*, Ann. **381,** 215; Ber. **45,** 2605):

$$(C_6H_5)_3C— + —NAr_2 = (C_6H_5)_3C—NAr_2$$

10. *p*-**Dimethylanilinodisulfide** reacts with triphenylmethyl in boiling xylene like the tetraarylhydrazines (*cf. 9*) although, according to *Lecher*, the disulfide is not decomposed into radicals at the temperature of the experiment (Ber. **48,** 527; *cf.* on the other hand, *Schönberg*, Ber. **66,** 1932, and p. 453):

$$2\,(C_6H_5)_3C— + (CH_3)_2N—C_6H_4—S—S—C_6H_4—N(CH_3)_2 = 2\,(C_6H_5)_3C—S—C_6H_4—N(CH_3)_2$$

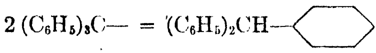
11. **Diazomethane,** which often acts as if it were free methylene, reacts with triphenylmethyl with formation of hexaphenylpropane (*Schlenk*, Ann. **394,** 183):

$$2\,(C_6H_5)_3C— + CH_2N_2 = [(C_6H_5)_3C]_2CH_2 + N_2$$

12. **Carbon monoxide,** contrary to expectations, does not react with triphenylmethyl. This is of some importance in connection with the valence relationships of carbon monoxide (*Schlenk,* Ber. **44,** 1176).

13. **Water** also does not react with triphenylmethyl (*Schlenk,* Ber. **44,** 1174). This is remarkable because many other compounds with mobile hydrogen react with triphenylmethyl, as shown in some of the following reactions (*15–19*).

14. **Hydrogen chloride** converts triphenylmethyl (in dry benzene solution) into *p*-benzhydryltetraphenylmethane (*Tschitschibabin,* Ber. **37,** 4709; **41,** 2421):



The explanation of this reaction, which is called, for short, *Tschitschibabin's* transformation, was of the greatest importance because for some time *p*-benzhydryltetraphenylmethane was mistaken for hexaphenylethane, and so hindered the true explanation of the colorless "ethane" form of triphenylmethyl. Besides the above-mentioned product, about 6% triphenylmethane and triphenylmethyl chloride are formed by the action of hydrogen chloride on triphenylmethyl (*Schlenk,* Ann. **372,** 8).

15. **Hydrogen chloride** acts on other triarylmethyls completely as described in the note above (*Schlenk,* Ann. **372,** 8; *Gomberg,* Am. **41,** 1655; **45,** 207):

$$Ar_3C\text{—} + HCl + \text{—}CAr_3 = Ar_3C\text{—}H + Cl\text{—}CAr_3$$

16. **Phenol** reacts with triphenylmethyl at 50° forming triphenylmethane and *p*-hydroxytetraphenylmethane (*Schmidlin,* Ber. **45,** 3180):

$$2\,(C_6H_5)_3C\text{—} + H\text{—}C_6H_4\text{—}OH = (C_6H_5)_3C\text{—}H + (C_6H_5)_3C\text{—}C_6H_4\text{—}OH$$

17. *o*- and *p*-**Xylene** at the boiling point react in the same way as phenol on triphenylmethyl:

$$2\,(C_6H_5)_3C\text{—} + H\text{—}C_6H_3(CH_3)_2 = (C_6H_5)_3C\text{—}H + (C_6H_5)_3C\text{—}C_6H_3(CH_3)_2$$

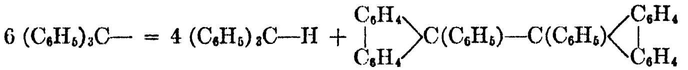
(*Wieland,* Ann. **401,** 237).

If *m*-xylene is used, *p*-benzhydryltetraphenylmethane is obtained in addition to triphenylmethane and some other unidentified products (*Wieland,* Ann. **401,** 236, 240).

18. **Phenylhydrazine** reacts even at ordinary temperature with triphenylmethyl, giving triphenylmethane and α,β-tritylarylhydrazines (*Schlenk,* Ber. **44,** 1175):

$$2\,Ar_3C\text{—} + H\text{—}NH\text{—}NH\text{—}Ar = Ar_3C\text{—}H + Ar_3C\text{—}NH\text{—}NH\text{—}Ar$$

19. **Disproportionation of triphenylmethyl.** The above-mentioned reactions (*15–18*) are related to the remarkable quantitative autodehydrogenation of triphenylmethyl, which takes place when the benzene solution is exposed for a long time (45 days) to diffuse daylight. Triphenylmethane and dibiphenylenediphenylethane are formed (*Schmidlin,* Ber. **45,** 1344; *Wieland,* Ann. **401,** 236; *Bowden,* J. **1928,** 1149):



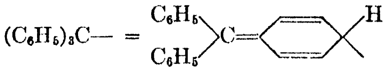
$$6\,(C_6H_5)_3C\text{—} = 4\,(C_6H_5)_3C\text{—}H + \left.\begin{array}{l}C_6H_4\\ |\\ C_6H_4\end{array}\right\rangle C(C_6H_5)\text{—}C(C_6H_5)\left\langle\begin{array}{l}C_6H_4\\ |\\ C_6H_4\end{array}\right.$$

20. Like the metals, triarylmethyls can mutually precipitate each other from solutions of their salts (*Schlenk*, Ann. **394,** 199):

$$(C_6H_5)_3C\text{—} + (C_6H_5\text{—}C_6H_4)_2(C_6H_5)C\text{—}Cl = (C_6H_5)_3C\text{—}Cl + (C_6H_5\text{—}C_6H_4)_2(C_6H_5)C\text{—}$$

21. **Molecular compounds.** *Gomberg* has shown that triphenylmethyl has a great tendency to form molecular compounds with the most varied substances (Ber. **38,** 1333, 2447; Am. **37,** 2569; *Rogers,* Am. **50,** 149). In nearly every case, two molecules of triphenylmethyl add on one molecule of the other substance. It has not yet been shown whether this is really a property of triphenylmethyl or of hexaphenylethane. The following substances combine with triphenylmethyl to give molecular compounds: (*a*) ketones other than acetone; (*b*) esters other than methyl and ethyl formate; (*c*) ethers and thioethers; (*d*) nitriles; (*e*) carbon disulfide; (*f*) chloroform; (*g*) amylene; (*h*) aromatic hydrocarbons (benzene and homologues); (*i*) hydroaromatic hydrocarbons (cyclohexane and methylcyclohexane); (*k*) paraffins (heptane, octane, decane, but not hexane). These compounds have considerable theoretical interest.

Quinoid nature of triarylmethyls? *Gomberg* proposed the concept (which has been much questioned) that, in solutions of hexaphenylethane, there was, in addition to dissociation, a tautomerization of triphenylmethyl to a quinoid form:



See *Walden,* Chem. der fr.Rad., p. 198 *ff.*, and *Gomberg,* Am. **47,** 2373; **48,** 1345; *Wooster,* Am. **51,** 1163; *Goldschmidt,* Ber. **53,** 47; *Ziegler,* Ann. **473,** 169 *ff.* According to *Ziegler* and others, there is no evidence for the existence of such a tautomeric equilibrium in the case of the triarylmethyls.

Effect of groups on the degree of association of triarylmethyls. It has been supposed for some time that the degree of association of the triarylmethyls depends on the electrochemical nature of the groups present. The question may be investigated by considering the basicity of the triarylmethanols (*Ziegler,* Ann. **458,** 229) and the determination of the conductivity of solutions (usually in liquid sulfur dioxide) of carbonium salts (determination of tendency of triarylmethyl chlorides and analogous compounds to tautomerize—connection with transition into solvated ionic state, *Ziegler,* Ann. **479,** 90). The results of these experiments made it possible to arrange the groups in a "basicity series." The following series, which is arranged with increasing positive action of the aryls, will serve as an example (*Ziegler,* Ann. **479,** 103):

C_6H_5—; β-$C_{10}H_7$—; *p*-C_6H_5--C_6H_4—; α-$C_{10}H_7$—;
p-CH_3—C_6H_4—; *o*-CH_3O—C_6H_4—; *p*-CH_3O—C_6H_4—;

In spite of the great number of investigations carried out in this direction, no simple connection has yet been traced between electrochemical character and tendency toward association of a radical (*Ziegler*, Ann. **479,** 116). At present we must be satisfied with the fact that the replacement of phenyl groups in triphenylmethyl by biphenylyl or naphthyl radicals decreases the tendency of the central carbon atom to association.

1. *Triarylmethyls*

Triphenylmethyl, trityl, $(C_6H_5)_3C$—, is yellow in solution, but colorless when crystalline (dimeric form), m.p. 145–147°, with a red coloration (*Gomberg,* Ber. **37,** 2037). Hexaphenylethane first gives a colorless solution, which becomes yellow owing to dissociation. For molecular weight determination, see *Schmidlin,* Ber. **45,** 3181; *Gomberg,* Am. **39,** 1652 (cryoscopic); *Schlenk,* Ann. **394,** 179 (b.p.). The degree of dissociation in benzene at 5.5° is about 2% and, at 80.5°, about 27%. In naphthalene at 79°, it is about 21%. The dissociation constant in naphthalene is 0.0028. The heat of dissociation of hexaphenylethane is 11.5 kcal. (*Ziegler,* Ann. **473,** 180). Velocity of dissociation and heat of activation of hexaphenylethane, see *Ziegler,* Ann. **504,** 131, 182. Colorimetric determinations with trityl solutions, see *Wieland,* Ann. **381,** 349; *Schmidlin,* Ber. **45,** 3181; *Ziegler,* Ann. **473,** 163. Absorption spectrum in organic solvents and liquid sulfur dioxide, *Meyer,* Ber. **44,** 2559; *Schlenk,* Ber. **46,** 1480. Electrical conductivity of liquid sulfur dioxide solutions, *Walden,* Z.physikal.Chem. **43,** 443, 451; *Gomberg,* Ber. **37,** 2045; **38,** 1342; *Schlenk,* Ann. **372,** 11. Heat of combustion at constant volume, 2377.7 kcal.; at constant pressure, 2380 kcal. Heat of formation, −71 kcal. (*Schmidlin,* C.r. **139,** 733; Ann.chim. [8], **7,** 251). Molecular volume of hexaphenylethane, *Ziegler,* Ann. **473,** 194. Methods of formation and chemical properties, see above. Peroxide, m.p. 185–186° (according to *Schmidlin,* m.p. 193°). For "*Schmidlin's* experiment" see p. 397.

TRITYLS WITH TOLYL RADICALS. Diphenyl-*p*-tolylmethyl, phenyl-di-*p*-tolylmethyl, and **tri-*p*-tolylmethyl.** These have only been obtained in solution. Their colors are orange-yellow, orange, and orange-red, respectively (*Gomberg,* Ber. **37,** 1626). Absorption spectrum of tri-*p*-tolylmethyl, *Meyer,* Ber. **44,** 2559. Peroxides, m.p. 170–171°, 147–148°, and 169–170°, respectively.

TRITYLS WITH BIPHENYLYL RADICALS. Diphenylmonobiphenylylmethyl, diphenyl-*p*-xenylmethyl, 4-**phenyltrityl,** $(C_6H_5)_2$-(p-$C_6H_5 \cdot C_6H_4)C$—, has only been obtained in solution (in benzene it is orange-red, and is about 15% dissociated at 5.5°) (*Schlenk,* Ann. **372,** 6; **394,** 186). Absorption spectrum, *Schlenk,* Ber. **46,** 1480. Peroxide, m.p. 180°.

Phenyldibiphenylylmethyl, phenyldi-*p*-xenylmethyl, (C_6H_5)-(p-C_6H_5—$C_6H_4)_2C$—, is red in solution (dissociated to the extent of about 80% in benzene at 5.5°), and is colorless in the solid state (dimer) (*Schlenk,* Ann. **372,** 6; Ber. **43,** 1756). Absorption spectrum, *Schlenk,* Ber. **46,** 1480.

Tribiphenylylmethyl, *tris-p*-**biphenylylmethyl, tri-*p*-xenylmethyl,** (p-C_6H_5—$C_6H_4)_3C$—, is only known in the monomolecular form. Solutions transmit deep violet light, but in thin layers the solution appears greenish. It forms greenish black crystals, melting at 186°. This was obtained by *Schlenk* as the first pure free organic radical (Ann. **372,** 1; Ber. **46,** 1475). Peroxide, m.p. 198°.

TRITYLS WITH NAPHTHYL RADICALS. Diphenyl-α-naphthylmethyl, $(C_6H_5)_2(\alpha$-$C_{10}H_7)C$—, is a greenish black powder (*Schlenk*, Ann. **394,** 193) and pale yellow crystals, m.p. 135–137° (*Gomberg*, Am. **39,** 1652; **41,** 1655). The solution in benzene (wine red) is about 59% dissociated at 5.5°. Dissociation constant in nitrobenzene, 0.06. In naphthalene at 79°, it shows ultradissociation. Molecular weight for the monomeric substance, calc. 293, found 264. Ultradissociation constant in naphthalene, 0.00114 (*Walden*, Chem. der fr.Rad., pp. 290, 300). Paramagnetic susceptibility, *G. N. Lewis*, Proc.Nat.Acad.Sci. **11,** 456. Peroxide, m.p. 172–173° (decomp.).

Phenylbiphenylyl-α-naphthylmethyl, $(C_6H_5)(p$-C_6H_5—$C_6H_4)(\alpha$-$C_{10}H_7)C$—, yellowish brown crystals; solution in benzene, deep reddish brown. In this solvent it shows ultradissociation at 5.5°. Molecular weight of the monomeric form, calcd. 369, found 348. Peroxide, m.p. 155° (*Schlenk*, Ann. **394,** 195; *Schmidlin*, Ber. **45,** 3183).

Dibiphenylyl-α-naphthylmethyl, $(p$-C_6H_5—$C_6H_4)_2(\alpha$-$C_{10}H_7)C$—, is very similar to the above (*Schlenk*, Ber. **46,** 1482).

Diphenyl-β-naphthylmethyl, $(C_6H_5)_2(\beta$-$C_{10}H_7)C$—, m.p. 135–140°, with a red coloration. Degree of dissociation in naphthalene at 79° about 47%. Dissociation constant in naphthalene 0.029, and in nitrobenzene 0.006. The following comparison of conductivity and color in liquid sulfur dioxide solution is interesting. Radicals arranged in order of decreasing conductivity: diphenyl-α-naphthylmethyl (green); diphenyl-β-naphthylmethyl (red); triphenylmethyl (orange-yellow). Diphenyl-β-naphthylmethyl peroxide, m.p. 166° (*Gomberg*, Am. **44,** 1810; *Ziegler*, Ann. **473,** 172).

Tri-β-naphthylmethyl, $(\beta$-$C_{10}H_7)_3C$—, crystallizes from its violet-red solution in crystals resembling chrome alum, and soon loses its color (even in carbon dioxide). In order to determine its molecular weight it must therefore be prepared in the Beckmann apparatus by the action of excess of silver on the chloro derivative. The values obtained are not very concordant, but indicate considerable dissociation (*Tschitschibabin*, J.pr. [2], **88,** 515).

HALOGENATED TRIARYLMETHYLS. Halogenated triphenylmethyls (Ber. **37,** 1633). ***p*-Chloro, *p*-bromo-,** and ***p*-iodotriphenylmethyl,** have been obtained only in solution (colors: wine red, orange-red, orange-red, respectively). Peroxides, m.p. 165°, 167°, 169°, respectively. **Tri-(*p*-chlorophenyl)-methyl,** $(p$-Cl—$C_6H_4)_3C$—, obtained only in solution, has a deep magenta color.

***p*-Bromo-diphenyl-1-naphthylmethyl,** $(C_6H_4Br)(C_6H_5)(\alpha$-$C_{10}H_7)$-C—, gives a violet solution. Peroxide, m.p. 146° (decomp.) **Diphenyl-4-bromo-1-naphthylmethyl,** $(C_6H_5)_2$ $(\alpha$-$C_{10}H_6Br)C$—, gives a brownish red solution. Peroxide, m.p. 153–154° (dec.). Poly-

meric peroxides have been obtained of both methyls, the formation being due to the action of oxygen on free radicals of the second order (*Gomberg*, Am. **45,** 1765).

NITRATED TRIARYLMETHYLS. Nitrated triphenylmethyls: mono-*p*-nitro, di-*p*-nitrotriphenylmethyl are only known in solution, in which both substances are deep green, and, in higher concentrations, red. They are very unstable compounds (*Ziegler*, Ann. **479,** 114). **Tri-(*p*-nitrophenyl)-methyl,** $(p\text{-}O_2N\text{—}C_6H_4)_3C\text{—}$, forms deep green crystals when viewed by reflected light. The crystals have a coppery luster, and are considerably dissociated (*Ziegler*, Ann. **458,** 254).

For other nitrated trityls, see under methoxylated triarylmethyls.

HYDROXYLATED TRIARYLMETHYLS. The experiments of *Gomberg* and his co-workers to obtain *p*-hydroxy- and *o*-hydroxytriphenylmethyl were subject to the interference of side reactions (Am. **37,** 2575; **45,** 190). The latter compound was obtained in the form of its peroxide, m.p. 131°. Recently it has been found possible to prepare, in solution, a triarylmethyl with a free hydroxyl group, **3-hydroxy-2-naphthyldiphenylmethyl,** $(HO)[3]C_{10}H_7[2]C(C_6H_5)_2$. This compound is deep brown in benzene solution, and exists to the extent of 85–90% in the radical form. Peroxide, m.p. 145° (*Gomberg*, Am. **47,** 2392).

METHOXYLATED TRIARYLMETHYLS. *o*-Methoxytriphenylmethyl, $(CH_3O)[2]C_6H_4[1]\underset{\cdot}{C}(C_6H_5)_2$, colorless in the solid form (m.p. 117–121°) gives an orange-red solution. Dissociation constant in benzene at 5.5°, about 26%. Dissociation constant in benzene, 0.0046. Peroxide, m.p. 160–161° (dec.) (*Gomberg*, Am. **45,** 190).

***p*-Methoxytriphenylmethyl,** $CH_3O[4]C_6H_4[1]\underset{\cdot}{C}(C_6H_5)_2$, is almost colorless (m.p. 145–150°), but gives an orange solution. Degree of dissociation in benzene at 5.5°, about 24%. Dissociation constant in benzene, 0.0029; in other solvents, see *Walden*, Chem.der fr. Rad., p. 291. Peroxide, m.p. 157° (*Gomberg*, Am. **45,** 207).

2,5-, 2,4-, and 3,4-**Dimethoxytriphenylmethyls,** are similar to the above. Only the first of these has been obtained in the solid state. Peroxides, m.p. 149°, 146°, 162.5°, respectively (*Gomberg*, Am. **47,** 2373).

***p*-Methoxy-*p*-nitrotriphenylmethyl, di-*p*-methoxy-mono-*p*-nitrotriphenylmethyl, mono-*p*-methoxydi-*p*-nitrotriphenylmethyl,** behave in exactly the same way as the mono- and di-*p*-nitrotriphenylmethyls described above.

BENZYLATED HYDROXYTRIPHENYLMETHYLS. The preparation of *o*-**benzyloxytriphenylmethyl,** is complicated by the interference of side-reactions, but the peroxide has been obtained, m.p. 153° (*Gomberg*, Am. 45, 207).

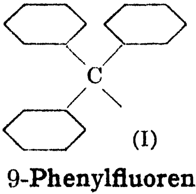
***p*-Benzyloxytriphenylmethyl,** $C_6H_5\cdot CH_2\cdot O[4]C_6H_4[1]\underset{\cdot}{C}(C_6H_5)_2$, is almost colorless (m.p. 142–145°), but it gives an orange-yellow solution. Degree of dissociation in benzene at 5.5°, about 34%. Dissociation constant in benzene 0.0056; in other solvents, see *Walden*, Chem.der fr.Rad., p. 292. Peroxide, m.p. 171° (*Gomberg*, Am. **45,** 207).

ACYLATED *p*-HYDROXYTRIARYLMETHYLS. Radicals of this kind have usually only been obtained in solution (cherry red). They are obtained from *p*-hydroxytriphenylmethyl by replacement of the phenolic hydrogen by carbethoxy, acetyl, or benzoyl groups. Peroxides, m.p. 171°, 172°, and 167° (dec.) (*Gomberg*, Am. **37**, 2575). The carbethoxy derivatives of the following methylated hydroxytrityls have been obtained: $HO[4]CH_3[3]C_6H_3[1]C(C_6H_5)_2$ and $HO[4]CH_3[2]C_6H_3[1]C(C_6H_5)_2$. Peroxides, m.p. 161–162°, 141–142° (decomp.) (*Gomberg*, Am. **38**, 1577; **39**, 1674).

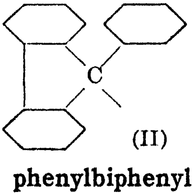
RADICALS OF THE BASIC TRIPHENYLMETHANE DYES. The preparation of the radicals of malachite green and crystal violet is of particular importance, because these compounds, contrary to all expectations, are only orange-yellow in color (in the cold; at 90°, they are orange-red) (*Wieland*, Ber. **55**, 1820, 1830; see method of formation *16*, p. 399). Both radicals, **bis-(*p*-dimethylamino)-triphenylmethyl** and ***tris*-(*p*-dimethylamino)-triphenylmethyl** cannot be distinguished in color in solutions of the same concentration. Their spectra show characteristic absorption bands. Like their colorless peroxides, they are very unstable. For their preparation from the triphenylmethane dyes, see *Conant*, Am. **53**, 676.

TRIARYLMETHYLS WITH CLOSED RINGS. From the constitutional point of view those triarylmethyls in which two aryl groups are linked together have a certain interest. There are very great differences between the capacity of the various compounds in this group to exist in the form of radicals. Ring closure, in itself, is without effect on the tendency toward association. If the linking between the two aryl groups is direct, practically the whole yield is in the form of the dimeric trityl with a fluorene linking. If, on the other hand, the aryls are linked with an intermediate polyvalent atom, trityls are formed in which the central atom is a member of a six-atom ring. Trityls with six-membered heterocyclic rings have been prepared in large numbers.

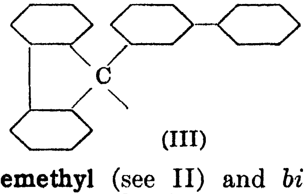
FLUORENYLS AND *bis*-FLUORENYLS. In spite of its close resemblance to triphenylmethyl (I), the trityl with a fluorene linking, derived from it (II), is, rather surprisingly, completely bimolecular (even in solution, at least at ordinary temperatures). Another surprising fact is that the replacement of the phenyl group in (II) by a biphenylyl radical (III) still further increases the tendency to association.



(I)



(II)



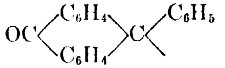
(III)

9-Phenylfluorenyl, phenylbiphenylenemethyl (see II) and ***bis*-(9-phenylfluorenyl)**, colorless crystals, m.p. 254°, give a brown coloration in boiling anisole or ethyl benzoate, which disappears on cooling (*Schlenk*, Ber. **43**, 1753). Molecular volume, *Ziegler*, Ann. **473**, 207. Peroxide, m.p. 193°.

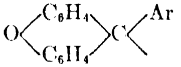
9-Anisylfluorenyl, anisylbiphenylenemethyl, and ***bis*-(9-anisylfluorenyl)**, colorless crystals, m.p. 227–230°. This compound behaves exactly in the same manner as the previous one on heating in solvents of high boiling point. It is noteworthy that apparently the tendency to association is not diminished in this case by the substitution of anisyl for phenyl, whereas the analogous change in the case of triphenylmethyl results in a considerable decrease in the association (p. 403). Peroxide, m.p. 192°, and red coloration, see *Schlenk*, Ann. **394,** 196.

9-Biphenylylfluorenyl, biphenylylbiphenylenemethyl (see formula III above), and *bis*-(**9-biphenylylfluorenyl**), colorless crystals, m.p. 175–176° (Ann. **372,** 30). In boiling anisole it develops a brown color, but less readily than 9-phenylfluorenyl (*Schlenk*, Ber. **43,** 1756). Peroxide, m.p. 193°.

HEXACYCLIC CLOSED-RING TRIARYLMETHYLS.* 10-**Phenylanthronyl** (I), a yellow crystalline powder, dissolving in benzene with a beautiful red color. Degree of dissociation in benzene at 5.5° about 33% (*Schlenk*, Ann. **394,** 191).

(I) 

$OC{<}^{C_6H_4}_{C_6H_4}{>}C{<}^{C_6H_5}$

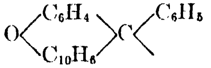
 (II)

$O{<}^{C_6H_4}_{C_6H_4}{>}C{<}^{Ar}$

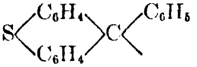
9-Arylxanthyls (II), yellow-colored, crystalline compounds, which dissolve in benzene with a deep red color (*Gomberg*, Ann. **370,** 158; *Schlenk*, Ann. **394,** 188; *Gomberg*, Am. **39,** 1652). Degree of dissociation of 9-phenylxanthyl in benzene at 80.5° is about 82%.

Xanthyl	M.p.	Dissociation constant in $C_{10}H_8$	M.p. of peroxide
Phenyl-	166–168°	0.049	219° (dec.)
p-Tolyl-	156–158°	0.050	212°
p-Chlorophenyl-	149–151°	0 029	213°

Further details of the dissociation of these compounds are given in *Walden*, Chem.der. fr.Rad., p. 288. α-**Naphthylxanthyl** is characterized by ultradissociation in naphthalene at 79°. Mol. wt. of the monomeric form: calc. 307, found 283 (see *Walden*, *loc. cit.* p. 301); m.p. 175–177°. Peroxide, m.p. 228–230° (decomp.). **9-Phenylpheno-β-naphthoxanthyl** (III), m.p. 212–214°, is distinguished from the above by the emerald-green color of its solutions. Peroxide, m.p. 229° (dec.).

(III) 

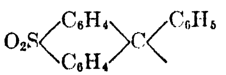
$O{<}^{C_6H_4}_{C_{10}H_6}{>}C{<}^{C_6H_5}$

 (IV)

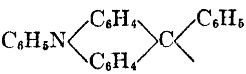
$S{<}^{C_6H_4}_{C_6H_4}{>}C{<}^{C_6H_5}$

9-Phenylthioxanthyl (IV), is brownish red in the solid form and in solution. Degree of dissociation in benzene at 5.5° about 14%. Peroxide, m.p. 187–188° (*Schlenk*, Ann. **394,** 190; *cf.* *Gomberg*, Am. **43,** 1940).

2,2′-**Sulfonidotriphenylmethyl** (V), a bright yellow crystalline substance melting at about 180° (dec.). Its solution is orange-red. Peroxide, m.p. 238–239° (dec.) (*Gomberg*, Am. **43,** 1945).

(V) 

$O_2S{<}^{C_6H_4}_{C_6H_4}{>}C{<}^{C_6H_5}$

 (VI)

$C_6H_5N{<}^{C_6H_4}_{C_6H_4}{>}C{<}^{C_6H_5}$

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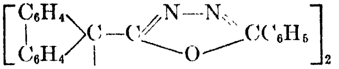
* Numbering according to *Beilstein*'s "Handbuch."

Diarylacridyls. Chloro-substitution products of 9-phenyl-N-phenylacridyl (VI), have been obtained in large numbers in solution, and have been separated in the form of their peroxides or iodides (*Gomberg*, Am. **48,** 1345).

2. Analogues of Trityl with Heterocyclic Substituents on the Central Atom

While in the above heterocyclic closed-ring triarylmethyls, the central carbon atom is itself a member of a hetero-ring, analogous trityls can be imagined in which heterocyclic radicals (in place of the benzene rings) are linked with the central atom. *Aspelund* (Acta Acad.Aboensis Math.Phys. 6, No. 12) has endeavored to obtain such compounds, by introducing the following heterocyclic ring systems into diphenylmethyl (or tetraphenylethane): 1,3,4-**oxadiazole,** 1,3,4-**thiadiazole,** 1,3,4-**triazole,** and 1,2,4,5-**tetrazine.** The compounds obtained were usually very unstable, and could be obtained, as a rule, only in the form of their peroxides or hydroquinone ethers. Only one oxadiazole derivative was obtained in the solid form, *viz.*, *bis*-(**biphenylene**)-*bis*-(**phenyloxadiazole**)-**ethane:**

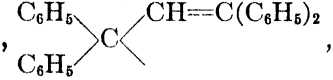


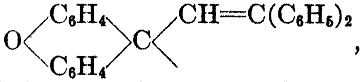
m.p. 227° (with red coloration and dec.). The benzene solution of the compound turned slightly red on warming, and a deeper red in bromobenzene. The coloration disappeared on cooling, and reappeared on warming. Although this is apparently a case of radical formation, the boiling solutions do not react with oxygen or iodine.

3. Trityls with Unsaturated Substituents

(C=C, C≡C, C=O, C≡N, conjugated to the central atom.)

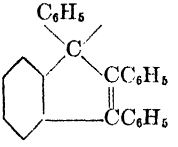
TRITYLS WITH OLEFINIC SUBSTITUENTS. The existence of this group of radicals indicates that the unsaturated nature of the attached group increases the tendency toward dissociation of the carbon atom combined with it. *Ziegler* has studied this class of compounds in detail. The possibility of valence tautomerism makes it difficult to assign a definite formula to them (for an attempted explanation on the basis of polycentricity see *Löwenbein*, Ann. **487,** 97).

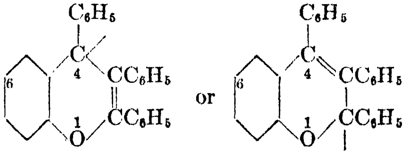
1,1,3,3-**Tetraphenylallyl,**  $\begin{array}{l}C_6H_5\\C_6H_5\end{array}\!\!>\!C\!<\!\begin{array}{l}CH{=}C(C_6H_5)_2\\ \\ \end{array}$, is a grass-green crystalline powder. Degree of dissociation in benzene at 5.5° about 80%. Peroxide (crude product), m.p. 146° (*Ziegler*, Ann. **434,** 50, 77). **Methoxylated tetraphenylallyls:** 1,1-dianisyl-3,3-diphenylallyl and 1,1-(*o,p,p'*-trimethoxydiphenyl)-3,3-diphenylallyl, are completely monomolecular in boiling benzene (*Ziegler*, Ann. **434,** 50, 72, 74).

9-(*β,β*-**Diphenylvinyl**)-**xanthyl,**  $O\!<\!\begin{array}{l}C_6H_4\\C_6H_4\end{array}\!\!>\!C\!<\!\begin{array}{l}CH{=}C(C_6H_5)_2\\ \\ \end{array}$, or **bi-[9-(*β,β*-diphenylvinyl)-xanthyl],** is a closed-ring tetraphenylallyl. The radical behaves very much like triphenylmethyl, so that the linking of two phenyl groups by oxygen has the reverse effect on the tendency towards association of tetraphenylallyl than it has on that of triphenylmethyl. The dixanthyl is a colorless, crystalline powder (m.p. 144–145°) which dissolves in benzene with a yellow color. The degree of dissociation in naphthalene at 79° is about 58%. The peroxide decomposes at 149–150° (*Ziegler*, Ann. **434,** 46, 65).

1,2,3-**Triphenylindenyl** (I), exists only in solution, which is colored orange-red. The peroxide decomposes at about 155° (*Kohler*, Am. Chem.J. **40,** 217). The compound may be regarded as a 1,1,2,3-tetraphenylallyl, in which the diphenylvinyl radical is linked with an aromatic nucleus.

(I)



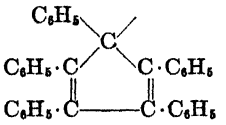


(II)

Chromenyls (and *bis*-chromenyls), examined by *Löwenbein* (Ann. **448,** 223) and *Ziegler* (Ann. **448,** 249; **473,** 172; **504,** 189), can be derived from the indenyls (see above) by inserting an oxygen atom into the five-membered ring. Two tautomeric formulas can be written for these radicals, in which they are regarded as either 4-chromenyls or 2-chromenyls. The chromenyls are colorless in the solid (dimeric) form, but are green in solution (in many solvents, yellow: *Ziegler*, Ann. **473,** 177).

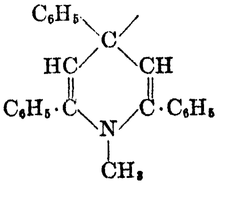
2,3,4-**Triphenylchromenyl** (II), and 2,3-**diphenyl-4-(α-naphthyl)-chromenyl.** Degree of dissociation in naphthalene at 79° about 45% and 65% (in 1% solution), respectively. Dissociation constants in naphthalene, 0.0051 and 0.0162, respectively. Peroxides, m.p. 152° and 171°, respectively. 2,3-**Diphenyl-4-benzylchromenyl** (m.p. 160°, dec.) breaks down at high temperatures (*e.g.*, in naphthalene at 79°; *Ziegler*, Ann. **448,** 233). 2,3-**Diphenyl-4-anisyl-6-methylchromenyl,** as well as 2,4-diphenylchromenyls (and *bis*-chromenyls) methylated in the 6-position, and having the following groups in the 3-position: H, CH_3, C_2H_5, C_3H_7, *iso*-C_3H_7, C_6H_5, CH_2-C_6H_5, have also been prepared.

Pentaphenylcyclopentadienyl (III), is a crystalline substance with a strong violet color, forming a very deep bluish red solution, m.p. 260°. Degree of dissociation in benzene at 5.5°, 100%. The extraordinary tendency towards dissociation of the central atom is obviously caused by the two olefinic groups, linked to each other. Since the pentaphenylcyclopentadienol, corresponding to the radical, is only slightly basic, it follows that the "widely accepted view that the basic character of the carbinol and the tendency to dissociation of the corresponding ethane are parallel," is wrong (*Ziegler*, Ann. **445,** 266).



(III)

(IV)



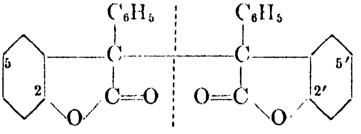
Dihydropyridyls can be derived from cyclopentadienylenes by introduction of an imino group. The best known is **N-methyl-2,4,6-triphenyldihydropyridyl** (IV). So far it has only been obtained in solution, the deep violet color of which indicates considerable dissociation (*Ziegler*, Ber. **59,** 242).

TRITYL ANALOGUES WITH A PHENYLACETYLENE RADICAL. 1,3,3,4,4,6-**Hexaphenylhexadiine,** $[C_6H_5—C{\equiv}C—\underset{\cdot}{C}(C_6H_5)_2]_2$, *sym*-diphenylethinyltetraphenylethane, m.p. 174–175°, with a red coloration. Rather surprisingly, this hydrocarbon shows only a slight tendency toward dissociation. Its solutions are colorless at 100°, but at higher temperatures become colored strongly orange-red (on cooling the reverse change slowly takes place). Degree of dissociation in camphor (*Rast*), about 3%. It is stable toward oxygen (*Wieland,* Ann. **470,** 205).

TRITYL ANALOGUES WITH BENZOYL GROUPS. Not only unsaturated hydrocarbon radicals, but also other substituents with reactive multiple bonds, can decrease the associative powers of a central carbon atom. *Goldschmidt* (Ber. **61,** 829) showed that mono-aryldibenzoylmethyl, $(C_6H_5)_2BrC—(p\text{-}C_6H_4)—\underset{\cdot}{C}(COC_6H_5)_2$, existed as a radical in its brownish red solution. The substance is obtained by the action of copper powder on diphenyldibenzoylxylylene bromide, $(C_6H_5)_2BrC—C_6H_4—CBr(COC_6H_5)_2$. The highly dissociated compound adds on bromine, the starting material being re-formed. It is decolorized by nitric oxide, but is not attacked by oxygen.

PUMMERER'S DEHYDROPHENOLS. These compounds may be regarded as radicals with trivalent carbon (α-ketomethyls) or as radicals with monovalent oxygen (aroxyls). It is very probable, however, that both forms exist together in tautomeric equilibrium, the aroxyl form predominating (Ber. **61,** 1102). Regarded as radicals with trivalent carbon, the compounds are related to those described above. Since, however, in their chemical properties, their aroxyl nature stands out most prominently, it has been considered better to deal with them under radicals with monovalent oxygen.

TRITYL ANALOGUES FROM ARYLATED SUCCINIC ACID DERIVATIVES. The following diphenyl-*bis*-coumaranone:



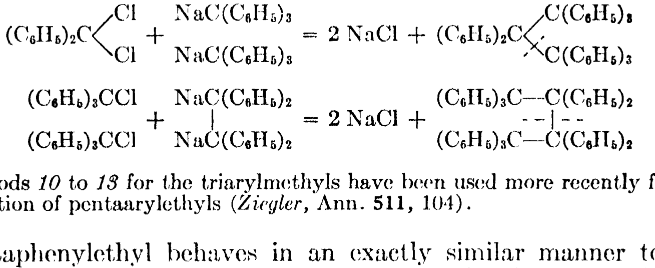
contains carbonyl groups, linked as in lactones. It is also known as 2,2′-**dihydroxytetraphenylsuccinic** *bis*-**lactone.** Some substitution products of this *bis*-lactone break down into blue to bluish violet radicals in boiling toluene. The 5,5′-dimethyl derivative of the above compound has been investigated the most carefully (m.p. 200–203° with bluish coloration). Degree of dissociation in toluene at 110°, about 20% (in 1% solution). Dissociation constant in toluene, 0.00109. The radicals are slightly affected by oxygen. Nitric oxide has no action (*Löwenbein,* Ber. **58,** 601).

Tetraphenylsuccinodinitrile behaves in a similar way. It dissociates at 140° into orange colored radicals (*Löwenbein*, Ber. **58**, 606; *Wittig*, Ber. **65**, 760; Ann. **513**, 26).

4. Other Trityl Analogues

PENTAARYLETHYLS. These radicals can be regarded as trityldiarylmethyls They show that the trityl radical in its capacity as an unsaturated substance affects the association of the central carbon atom. The investigation of these theoretically very important radicals is due to *Schlenk* and *Mark* (Ber. **55**, 2285, 2299). **Pentaphenylethyl** is known only in the monomolecular form. Since the dissociation of the dimer of this compound is in contradiction to the *Thiele-Werner* principle (p. 389), its investigation led the discoverers to propose new views on the nature of the carbon bond (Ann. **437**, 208; **487**, 97).

Pentaphenylethyl, $(C_6H_5)_2\dot{C}—C(C_6H_5)_3$, forms golden yellow crystals with a weak metallic luster. Degree of dissociation in benzene at 5.5°, about 100%. Pentaphenylethyl is prepared by method *5* (p. 394) from octaphenylpropane or decaphenylbutane. The hydrocarbons produced then dissociate with formation of pentaphenylethyl:

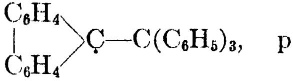


$$(C_6H_5)_2C\begin{matrix}\diagup Cl\\ \diagdown Cl\end{matrix} + \begin{matrix}NaC(C_6H_5)_3\\ NaC(C_6H_5)_3\end{matrix} = 2\,NaCl + (C_6H_5)_2C\begin{matrix}\diagup C(C_6H_5)_3\\ \diagdown C(C_6H_5)_3\end{matrix}$$

$$\begin{matrix}(C_6H_5)_3CCl\\ +\\ (C_6H_5)_3CCl\end{matrix}\quad\begin{matrix}NaC(C_6H_5)_2\\ |\\ NaC(C_6H_5)_2\end{matrix} = 2\,NaCl + \begin{matrix}(C_6H_5)_3C—C(C_6H_5)_2\\ |\\ (C_6H_5)_3C—C(C_6H_5)_2\end{matrix}$$

Methods *10* to *13* for the triarylmethyls have been used more recently for the preparation of pentaarylethyls (*Ziegler*, Ann. **511**, 104).

Pentaphenylethyl behaves in an exactly similar manner to triphenylmethyl (addition of oxygen, chlorine, and sodium, not affected by water). Pentaphenylethyl chloride is very readily hydrolyzed and breaks down, even at 35°, into the radical and chlorine (*cf.* the behavior of triphenylmethyl iodide). The radical can also be obtained from the chloride by the action of copper-bronze.



1-Biphenylene-2-triphenylethyl-(1), $\begin{matrix}C_6H_4\diagdown\\ |\quad\;\;\\ C_6H_4\diagup\end{matrix}\dot{C}—C(C_6H_5)_3$, prepared from fluorenone chloride and triphenylmethyl sodium, forms violet crystals which give a dark red solution. Degree of dissociation in benzene at 5.5°, about 100%. It is noteworthy that the increase in tendency to association produced in biphenylenephenylmethyl by the biphenylene radical, is not reproduced in biphenylenetriphenylethyl.

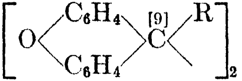
DIARYLALKYLMETHYLS (and **TETRAARYLDIALKYLETHANES**). **Diphenyl-*tert*-butylmethyl,** $(C_6H_5)_2\dot{C}—C(CH_3)_3$, m.p. 138–141°. Solutions of this hydrocarbon are only slightly colored, but on warming to 50° they become lemon yellow. On cooling the color fades again. Although the solutions are very sensitive to oxygen, the powerful effect of the triphenylmethyl radical on the dissociation of the central carbon atom in pentaphenylethyl, is not reproduced by its aliphatic analogue (the *tert*-butyl radical) (*Conant*, Am. **50,** 2041). **Di-*p*-xenyl-*tert*-butylmethyl,** $(C_6H_5{\cdot}C_6H_4)_2\underset{\cdot}{C}—C(CH_3)_3$, a bright orange crystalline substance, m.p. 136–137°, gives orange-red solutions even at ordinary temperature. Degree of dissociation in benzene at 5.5°, about 70%. Comparison with the behavior of the foregoing compound shows clearly the effect of the xenyl groups on dissociation (*Conant*, Am. **55,** 2098).

The radicals $(C_6H_5)_2\underset{\cdot}{C}—CH_3$ and $(C_6H_5)_2\underset{\cdot}{C}—C_2H_5$ are only known in the dimeric forms, as colorless crystalline substances, and are therefore to be called tetraphenyldialkylethanes (*Ziegler*, Ann. **437,** 227). 1,1,2,2-**Tetraphenyldimethylethane** (= 2,2,3,3-tetraphenylbutane), m.p. 126–127°, is completely stable toward air and halogens at room temperature. The ethane binding can however be split by potassium, and at higher temperatures it dissolves with disproportionation into 1,1-diphenylethane and 1,1-diphenylethylene. **Tetraphenyldiethylethane** (= 3,3,4,4-tetraphenylhexane), m.p. 85–86°, shows a similar decomposition in benzene solution, even at 5°, proceeding at a measurable velocity, and attempts to make tetraphenyldibenzylethane have failed, presumably on account of the even increased tendency to disproportionate in this manner.

sym-**Diphenyltetrabenzylethane,** m.p. 126–127°, is a colorless hydrocarbon, which shows no tendency to dissociation or disproportionation even at high temperatures. It follows that the effect of benzyl groups on the dissociation tendency of an ethane is very small (*Ziegler*, Ann. **437,** 235).

CLOSED RING DIARYLALKYLMETHYLS (and DIMERS).

XANTHYLS and **DIXANTHYLS,**



$\left[O\genfrac{}{}{0pt}{}{\diagup C_6H_4 \diagdown}{\diagdown C_6H_4 \diagup}\overset{[9]}{C}\genfrac{}{}{0pt}{}{\diagup R}{\diagdown}\right]_2$

. Compounds of the above formula (R = non-aromatic radical) in contrast to the already described substances alkylated in the 9-position, show a small tendency to dissociation. *Conant* and his co-workers (Am. **51,** 1925, and earlier papers) have prepared a large number of these dixanthyls, and have examined their solutions on heating (occurrence of color) and the action of oxygen on them. If the substituent (R) is linked to the central carbon atom by primary carbon, the dixanthyls are colorless, crystalline substances, the solutions only becoming colored at high temperatures (*e.g.*, for R = CH_3, at 160°). If, however, the substituent (R) is linked to the central carbon atom by secondary carbon, the dixanthyls are yellow powders, whose solutions are cherry red in color even at ordinary temperature. In contrast to dixanthyl itself (R = H) the compounds are generally affected by oxygen (the absorption velocity corresponding to degree of dissociation). The following dixanthyls with a primarily linked carbon atom have been investigated: R = $CH_3—$, $CH_3CH_2—$, $(CH_3)(CH_2)_3—$, $(CH_3)(CH_2)_5—$, $(CH_3)_2CHCH_2—$, $(CH_3)_2CH(CH_2)_2—$, $C_6H_5CH_2—$, $(C_6H_5)(CH_2)_2—$, $C_6H_5(CH_2)_3—$, *p*-$ClC_6H_4CH_2—$, α-$C_{10}H_7CH_2—$. The following with a secondarily linked carbon atom have been investigated: R = $(CH_3)_2CH—$, $(CH_3)(C_2H_5)CH—$, and cyclohexyl. Other examples of dixanthyls (R = —COOH and —$COOCH_3$) (*Conant*, Am. **47,** 572, 3068; **48,** 1743; **49,** 2080).

PENTA- and **TETRAARYLETHANES.** **Pentaphenylethane,** $(C_6H_5)_3C—CH(C_6H_5)_2$, m.p. 179°, is colorless both in the solid state and in solution. It is split at the ethane linkage by potassium. On boiling in solvents of high boiling point it dissociates according to the equation:

$$2\,(C_6H_5)_3C—CH(C_6H_5)_2 = 2\,(C_6H_5)_3C— + (C_6H_5)_2HC—CH(C_6H_5)_2$$

It follows that lack of a "third" aryl group on one side does not hinder dissociation into radicals, but lack of a "third" aryl group on both sides increases the tendency to dissociation (for another view of the reaction, see *Goldschmidt*, Ber. **53,** 53). It is to be particularly noted that this holds not only for 1,1,2,2-**tetraphenylethane** (b.p. 380°), but also for 1,1,2,2-**tetrabiphenylylethane** (m.p. 276–279°), which by analogy one would expect to show a tendency to dissociate (*Schlenk*, Ber. **43,** 3541; **44,** 1180; **47,** 1760; see, on the other hand, *Schoepfle*, Am. **52,** 4021, where the supposed occurrence of free, red benzhydryl is reported).

The following results obtained by *Paneth* show, however, that it is only a question of degree.

5. *Alkyls*

Literature: *F. O. Rice* and *K. K. Rice*, The Aliphatic Free Radicals, Oxford University Press.

Paneth and his co-workers have shown that the radicals methyl and ethyl do exist, though they may be short-lived (Ber. **62,** 1335; **64,** 2702, 2708; Z.Elektrochem. **37,** 577; see also *Pearson*, Nature **129,** 832). According to these authors, the higher alkyls tend strongly to decompose into the lower homologues (*Paneth*, Ber. **64,** 2707; *Rice*, Am. **54,** 3529). On the other hand when hexane and cyclohexane are submitted to the action of cathode rays, the mass spectrogram shows new lines indicating the intermediate formation of higher alkyls (*Conrad*, Trans.Faraday Soc. **30,** 215). *Rice* (Trans.Faraday Soc. **30,** 152; Am. **56,** 1311) has obtained the methyl and ethyl radicals (but not the higher homologues) by thermal decomposition of the most diverse aliphatic compounds, and has determined the heats of activation of the dissociation (*e.g.*, $H_3C—CH_3 \longrightarrow 2\,—CH_3 = 79$ kcal.). See *Fraser*, Trans.Faraday Soc. **30,** 182, and *Bone*, *ibid.* **30,** 148.

Methyl, —CH_3, is obtained, according to *Paneth*, by the thermal decomposition of lead tetramethyl (or bismuth trimethyl) under reduced pressure, in a stream of hydrogen or nitrogen:

$$Pb(CH_3)_4 \xrightarrow{\text{heat}} Pb + 4\,CH_3—$$

CH_3— carried over with the gas may be made to dissolve films of metals (Pb, Bi, Sb, Zn) by the reverse reaction. The fact that the power to remove these metallic mirrors decreases rapidly with distance from the generating apparatus shows the great tendency of methyl to associate to dimethyl. From the time required to remove an antimony mirror by a stream of hydrogen containing methyl under definite experimental conditions the half-life of free methyl has been calculated to be 10^{-3} sec. Recently use has been made of the above-described method of obtaining methyl for synthetic purposes (*Fraser*, Trans.Faraday Soc. **30,** 182).

Other methods of formation: Propane, butane, and acetone decompose at 800–1000° with formation of methyl (*Rice*, Am. **54,** 3529). The thermal decomposition of azomethane also gives methyl (*Leermakers*, Am. **55,** 3499). The radical is also formed by the decomposition of methyl bromide vapor with sodium vapor (*Polanyi*, Z.physikal. Chem. **B23,** 291).

Ethyl, $-CH_2-CH_3$, is obtained by the thermal decomposition of lead tetraethyl (*Paneth*, Ber. **64,** 2702), and by the action of sodium vapor on ethyl bromide vapor (*Polanyi, loc. cit.*) It is produced together with larger quantities of methyl by the thermal decomposition of propane and butane (*Rice*, Am. **54,** 3529). In its properties it completely resembles the lower homologue. Its half-life is of the same order.

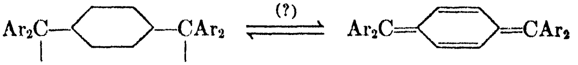
For higher alkyls, see above.

The formation of free phenyl by the thermal decomposition of phenylazotriphenylmethane (*Wieland*, Ber. **55,** 1816), and of lead tetraphenyl and other metallic phenyls (*Shurov*, Ber. **65,** 1507; *Dull*, Am. **55,** 3898) should also be mentioned. An investigation of the thermal dissociation of cyanogen into the cyanide radical has also been carried out (*Kistiakowsky*, J.Chem.Phys. **1,** 432)

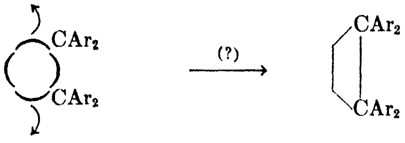
6. *Diradicals of the Trityl Type*

These compounds are of interest because of theoretical problems:

1. Because of the possible tautomerism between the diradicals and the quinone-dimethides (nomenclature, see *Pummerer*, Ber. **52,** 1392) (and analogous "binding isomers," Ann. **483,** 144; *cf. Schlenk*, Ber. **52,** 8, and *Müller*[*]):



2. Because of the possible effect of ring strain on the formation of such diradicals (*Wittig* and co-workers, Ann. **505,** 17, and earlier papers):



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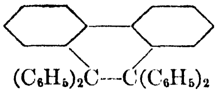
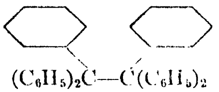
[*] N. **22,** 335; Z.Elektrochem. **40,** 542; Ann. **517,** 134. The author maintains that *p,p'*-biphenylene-*bis*-(diphenylmethyl), dibenzyl-*p,p'*-*bis*-(diphenylmethyl), *lin*-dibenzanthracene, and irradiated rubrene are diamagnetic, which is contrary to the assumed diradical formula (considerable displacement of the equilibrium in favor of the quinoid isomers). *m,m'*-Biphenylene-*bis*-(diphenylmethyl) is, on the other hand, according to the magnetic method, 6 ± 2% dissociated into the diradical in 9% benzene solution at 74°.

BENZENE DERIVATIVES. ***o*-Compound,** $(C_6H_5)_2\underset{\cdot}{C}[1]C_6H_4[2]\underset{\cdot}{C}(C_6H_5)_2$, isomerizes in the nascent state to **9,9,10-triphenyldihydroanthracene,** m.p. 224–226.5° (*Wittig*, Ber. **64,** 2395). The *m*-compound (obtained in solution) is deep violet, and reacts with oxygen. It is **tetraphenyl-*m*-xylylene,** $(C_6H_5)_2\underset{\cdot}{C}[1]C_6H_4[3]\underset{\cdot}{C}(C_6H_5)_2$ (*Schlenk*, Ber. **48,** 661). The *p*-compound, which is orange in color and is not affected by oxygen, must be regarded as **quinonetetraphenyldimethide,** $(C_6H_5)_2C{:}[1]C_6H_4[4]{:}C(C_6H_5)_2$ (*Thiele*, Ber. **37,** 1463).

BIPHENYL DERIVATIVES. The *o,o'*-compound, $(C_6H_5)_2\underset{\cdot}{C}[o]C_6H_4.C_6H_4[o']\underset{\cdot}{C}(C_6H_5)_2$, m.p. 339.5–341°, behaves like **9,10-tetraphenyldihydrophenanthrene** (I), of which the constitutional similarity to hexaphenylethane (II) is noteworthy. The ethane linkage of this substance (I) is easy to open, *e.g.*, by potassium, but not by oxygen (*Wittig,* Ann. **505, 17**):

(I)





(II)

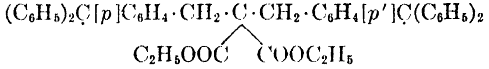
The introduction of two methoxy groups in the two unoccupied *o*-positions of the biphenyl nucleus of (I) does not change the chemical nature of the compound (m.p. 232°), although on the basis of the distorted position of the biphenylbenzene nuclei, radical dissociation would be expected. The *m*-compound corresponding to the first-mentioned compound is the diradical ***m,m'*-biphenylene-*bis*-(diphenylmethyl),** or di-*m*-trityl, $(C_6H_5)_2\underset{\cdot}{C}[m]C_6H_4.C_6H_4[m']\underset{\cdot}{C}(C_6H_5)_2$. It is almost colorless (dimeric), but dissolves giving an orange-red solution. Degree of dissociation in benzene at 5.5°, about 10% (in 3% solution). The compound is attacked by oxygen (*Schlenk*, Ber. **48,** 725). The corresponding *p*-compound is completely radical in nature. It was the first diradical to be discovered (*Tschitschibabin*, Ber. **40,** 1810). ***p,p'*-Biphenylene-*bis*-(diphenylmethyl),** or di-*p*-trityl, $(C_6H_5)_2\underset{\cdot}{C}[p]C_6H_4\cdot C_6H_4[p']\underset{\cdot}{C}(C_6H_5)_2$, is solid, and dissolves giving a deep reddish violet solution (see also *Schlenk*, Ber. **48,** 723). ***p,p'*-Biphenylene-*bis*-(dibiphenylylmethylyl),** or *p,p'*-xenylene-*bis*-(dixenylmethyl), $(C_6H_5\cdot C_6H_4)_2\underset{\cdot}{C}[p]C_6H_4\cdot C_6H_4[p']\underset{\cdot}{C}(C_6H_4\cdot C_6H_5)_2$, resembles the above hydrocarbon closely, but forms a deep blue solution (*Schlenk*, Ber. **48,** 721).

DIPHENYLMETHANE DERIVATIVES. **Diphenylmethane-*p,p'*-*bis*-(diphenylmethyl),** or *p,p'*-*bis*-(diphenylmethyl)-diphenylmethane, or di-*p*-tritylmethane, $(C_6H_5)_2\underset{\cdot}{C}[p]C_6H_4\cdot CH_2\cdot C_6H_4[p']\underset{\cdot}{C}(C_6H_5)_2$, is almost completely colorless in the dimeric solid form but dissolves with a fiery red color. Degree of dissociation in benzene at 5.5°, about 70–80%. The compound is sensitive to light and oxygen (the oxidation product is monomolecular) (*Wittig,* Ber. **61,** 854).

1,2-**DIPHENYLETHANE DERIVATIVES.** **Dibenzyl-*p,p'*-*bis*-(diphenylmethyl),** *p,p'*-*bis*-(diphenylmethyl)-α,β-diphenylethane, or 1,2-di-*p*-tritylylethane, $(C_6H_5)_2\underset{\cdot}{C}[p]C_6H_4\cdot CH_2\cdot CH_2\cdot C_6H_4[p']\underset{\cdot}{C}(C_6H_5)_2$, forms deep bluish violet solutions, resembling otherwise the above-described compound. **Dibenzyl-*p,p'*-*bis*-(1-phenylethyl),** CH_3-

$(C_6H_5)\underset{\cdot}{C}[p]C_6H_4\cdot CH_2\cdot CH_2\cdot C_6H_4[p']\underset{\cdot}{C}(C_6H_5)(CH_3)$, has been obtained only in the trimeric form (colorless powder, m.p. 110–115°) (*Wittig*, Ber. **61,** 854).

1,3-DIPHENYLPROPANE DERIVATIVES. 1,3-Diphenyl-2,2-dicarbethoxypropane, *p,p′-bis*-**(diphenylmethyl),** 1,3-di-*p*-tritylyl-2,2-dicarbethoxypropane:



$$(C_6H_5)_2\underset{\cdot}{C}[p]C_6H_4\cdot CH_2\cdot \underset{C_2H_5OOC\quad COOC_2H_5}{C}\cdot CH_2\cdot C_6H_4[p']\underset{\cdot}{C}(C_6H_5)_2$$

has been obtained only in (bright brown) solution which is slowly decolorized by oxygen (*Wittig.*, Ber. **62,** 1405).

1,4-DIPHENYLBUTANE DERIVATIVE. 1,4-Diphenylbutane-*p,p′-bis*-**(diphenylmethyl),** *α,δ-bis*-[*p*-(diphenylmethyl)-phenyl]butane, or 1,4-di-*p*-tritylylbutane, $(C_6H_5)_2\underset{\cdot}{C}[p]C_6H_4(CH_2)_4C_6H_4[p']\underset{\cdot}{C}(C_6H_5)_2$, dissolves with a yellow color. Its degree of dissociation is small (*Wittig*, Ber. **62,** 1410).

BUTADIENE and **BUTANE DERIVATIVES. 1,1,4,4-Tetraphenylbutadiene-1,3,** $(C_6H_5)_2C{:}CH.CH{:}C(C_6H_5)_2$, is colorless, m.p. 201°, and is obtained directly from the nascent diradical $(C_6H_5)_2\underset{\cdot}{C}\cdot CH{:}CH\cdot\underset{\cdot}{C}(C_6H_5)_2$. The diradical, $(C_6H_5)_2\underset{\cdot}{C}\cdot CH_2\cdot CH_2\cdot\underset{\cdot}{C}(C_6H_5)_2$, decomposes immediately in the nascent state with formation of two moles of *asym*-diphenylethylene, but can be obtained by the action of oxygen in the form of the crystalline, cyclic peroxide, 3,3,6,6-tetraphenyldioxane-1,2, m.p. 171–180° (*Wittig*, Ber. **61,** 1627).

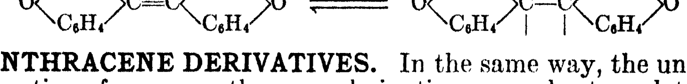
It is possible that the compound originally regarded as **tetraphenylcyclobutanedione**-1,2, which is obtained by the thermal decomposition of benzilic acid, and which forms deep red crytals, m.p. 168° (Ber. **61,** 941) is really the ring-opened diradical **oxalyl-***bis*-**(diphenylmethyl),** $(C_6H_5)_2\underset{\cdot}{C}\cdot CO\cdot CO\cdot\underset{\cdot}{C}(C_6H_5)_2$ (*Langenbeck*, Ber. **62,** 962).

Diradicals of the Trityl Type as Tautomeric Unsaturated Compounds

Dixanthylene, dichromylene. For the explanation of the thermochromic properties of certain closed-ring tetraarylethylenes and similar compounds, the tautomeric equilibrium:

$$:C{=}C: \rightleftharpoons :\underset{\vdots}{C}-\underset{\vdots}{C}:$$

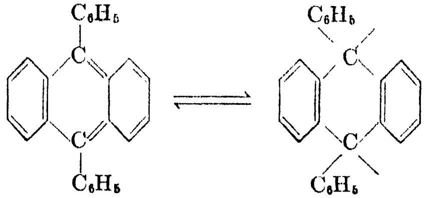
is assumed (*Schönberg*, Ber. **64,** 2323), *e.g.*, for dixanthylene.



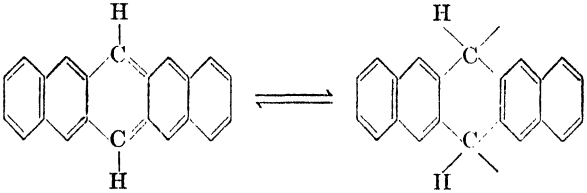
ANTHRACENE DERIVATIVES. In the same way, the unusual properties of many anthracene derivatives may be traced to the equilibrium:

$$:C{=}C-C{=}C: \rightleftharpoons :\underset{\vdots}{C}-C{=}C-\underset{\vdots}{C}:$$

This holds, for example, in the case of 9,10-**diphenylanthracene** (*Ingold*, J. **1926,** 3080).

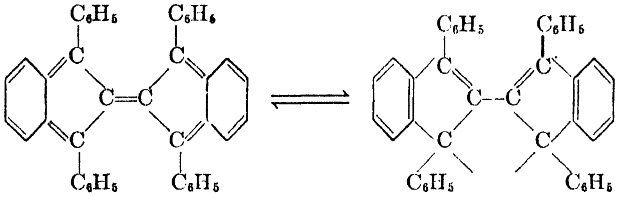


Particular interest attaches to the analogous behavior of the blue ***lin*-dibenzanthracene,** since in this case a hydrogen atom would be attached directly to a trivalent carbon atom which has not been previously observed (*Clar*, Ber. **63**, 2967).



For analogous behavior (the "diyl-state") in the case of other aromatic hydrocarbons, see *Clar*, Ber. **66**, 202, and earlier papers.

Rubrene (= 1,1′,3,3′-tetraphenylrubrene; see *Dufraisse*, Ber. **67**, 1021; *Schönberg*, Ber. **68**, 162; Vol. III, p. 602). This orange hydrocarbon possesses the remarkable property of combining with oxygen in the light giving a colorless peroxide, which, on warming, splits off the oxygen again, and is converted back into rubrene with emission of light. The behavior of rubrene towards oxygen is to be ascribed to tautomerism between a conjugated system of five ethylene linkages with a diradical form (*Schönberg*, Ber. **67**, 1404; *Dufraisse*, Ber **67**, 2018; *Schönberg*, Ber. **68**, 162).



(b) Other Types of Compounds with Trivalent Carbon

We shall here deal with those compounds of which the trivalent carbon atom is not only linked with other carbon atoms, but often is attached to other groups which are connected to it by means of a hetero-atom. The most important class of these compounds is that of the metal ketyls.

1. Metal Ketyls ($Ar_2\underset{\cdot}{C}$—O—K *and Analogues*)

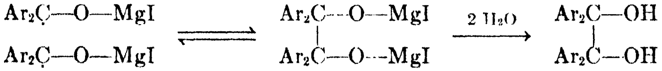
The metal ketyls were regarded by *Schlenk* as compounds containing trivalent carbon, although *Beckmann*, their discoverer, and *Acree* had before him investigated these substances, which are very difficult to work with (*Erlenmeyer*, Ann. **266,** 1; *Acree*, Am.Chem.J. **29,** 588; *Schlenk*, Ber. **44,** 1182; **46,** 2840; **47,** 486; Ann. **464,** 22).

For the supposed occurrence of a radical of the type $R_2\underset{|}{\underset{\cdot}{C}}{-}OH$, see Ber. **65,** 1625.

METHODS OF FORMATION. *1.* The simplest method of preparing the metal ketyls depends on the action of metals (K, Na, Li) on the diaryl ketones (in indifferent solvents under nitrogen: *Schlenk*, Ber. **46,** 2843; *Schlubach*, Ber. **48,** 12):

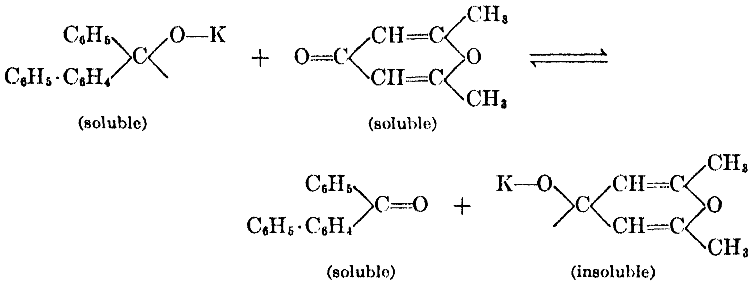
$$Ar_2C{=}O + K \rightleftharpoons Ar_2\underset{\cdot}{C}{-}O{-}K$$

Diaryl ketones are also attacked by magnesium + magnesium iodide, and by Be + BeI_2, and by magnesium amalgam. In the first case iodomagnesium ketyls are first formed (presumably with intermediate formation of MgI), and this is accompanied by the formation of an intense color. The dimers of these ketyls give pinacones by hydrolysis (*Schlenk*, Ber. **46,** 2847; *Gomberg*, Am. **49,** 236, 2584; **51,** 2229):

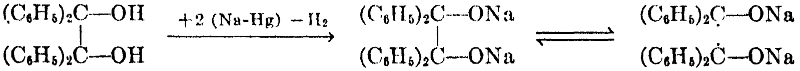


$$\begin{array}{l}Ar_2\underset{\cdot}{C}{-}O{-}MgI\\ Ar_2\underset{\cdot}{C}{-}O{-}MgI\end{array} \rightleftharpoons \begin{array}{l}Ar_2C{-}O{-}MgI\\ \quad\;|\\ Ar_2C{-}O{-}MgI\end{array} \xrightarrow{2\,H_2O} \begin{array}{l}Ar_2C{-}OH\\ \quad\;|\\ Ar_2C{-}OH\end{array}$$

2. Another method which is particularly suitable for the preparation of insoluble metal ketyls (*e.g.*, dimethylpyrone potassium) consists in the reaction between the ketone concerned, and phenyl biphenylyl ketone potassium, which is readily soluble in ether (*Schlenk*, Ber. **46,** 2846):

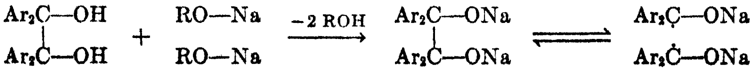


3. Metal ketyls are formed from aromatic pinacones by the action of sodium amalgam, hydrogen being evolved (*Schlenk*, Ber. **44,** 1184):



$$\begin{array}{l}(C_6H_5)_2C{-}OH\\ \qquad\;\;|\\ (C_6H_5)_2C{-}OH\end{array} \xrightarrow{+2\,(Na\text{-}Hg)\,-\,H_2} \begin{array}{l}(C_6H_5)_2C{-}ONa\\ \qquad\;\;|\\ (C_6H_5)_2C{-}ONa\end{array} \rightleftharpoons \begin{array}{l}(C_6H_5)_2\underset{\cdot}{C}{-}ONa\\ (C_6H_5)_2\dot{C}{-}ONa\end{array}$$

4. Another very similar method depends on the reaction of aromatic pinacones with (alcoholic) sodium alcoholates. Alcohol is a by-product (*Schlenk*, Ber. **46,** 2841):



$$\begin{array}{l}Ar_2C{-}OH\\ \quad\;|\\ Ar_2C{-}OH\end{array} + \begin{array}{l}RO{-}Na\\ RO{-}Na\end{array} \xrightarrow{-2\,ROH} \begin{array}{l}Ar_2C{-}ONa\\ \quad\;|\\ Ar_2C{-}ONa\end{array} \rightleftharpoons \begin{array}{l}Ar_2\underset{\cdot}{C}{-}ONa\\ Ar_2\dot{C}{-}ONa\end{array}$$

TECHNIQUE. The preparation of the metal ketyls (and other very reactive radicals) can be carried out by a process devised by *Schlenk* (Ber. **46**, 2843), which will be quoted here from the original paper (*cf. Ziegler*, Ann. **437**, 242):

"Air, moisture, and carbon dioxide must be rigidly excluded in the preparation of the metal ketyls. The work was therefore carried out in a current of nitrogen, which in order to purify it, was first passed over a long layer of soda-lime. It was then freed from the last traces of oxygen by passing it over reduced copper in a strongly heated quartz tube, and was finally completely dried by passing through a large drying apparatus containing sulfuric acid and phosphorus pentoxide. Since rubber tubing gives up moisture to a dried current of gas, it is necessary to pass the gas through drying tubes recently filled with phosphorus pentoxide.

"The preparation of a metal ketyl, *e.g.*, phenyl biphenylyl ketone potassium, is carried out as follows. In a glass vessel (Fig. 1, p. 418), with a volume of about 150 cc., is placed about 1 g. of pure, well-dried, phenyl biphenylyl ketone, and about 120 cc. of ether freshly dried with sodium. The air is completely replaced by nitrogen which enters at *a*. When this is the case, about 1 g. of potassium is added through *b*, the metal having been cut into thin pieces under dry benzene. The liquid immediately begins to assume a dark green color. Tube *b* is now drawn off to a capillary in the blowpipe, a continuous current of nitrogen being maintained through *a*. The nitrogen stream is then turned off by pinching the rubber tube with the fingers at *a*, and *b* is sealed off. The tubing is then disconnected at *a*, and this capillary is sealed.

"The vessel *A* is then strongly shaken for 4 to 5 hours in a shaking machine. It can then be assumed that all the ketone will have been converted into the potassium compound.

"The solution must now be filtered, and this is accomplished in the following way. Capillary *b* is scratched with a file, and the tubing connected to the nitrogen apparatus is pushed over the tube so that it grips the neck of vessel *A* firmly. With the nitrogen current connected, the capillary is broken inside the rubber tubing by slight pressure. Tube *a* is then broken near the capillary. Nitrogen then circulates through *A* from *b* to *a*, and no air has been admitted.

"Vessel *A* is now connected with a filtering apparatus, *C*, as shown in Fig. 2. This consists of an ordinary adaptor with a Soxhlet thimble, *c*. This filter can be folded from ordinary filter paper by wrapping it round a test tube, and must be specially dried before use. This is best carried out by connecting apparatus *C* and the filter paper in position to a filter pump, and warming the tube with a Bunsen burner until the paper just begins to turn yellow.

"When the nitrogen has been passing through the apparatus sufficiently long to have removed all the air from it, the apparatus is tilted so that the liquid from *A* filters into *B*. A convenient piece of apparatus for doing this is shown in Fig. 3. When the liquid has filtered into *B*, a second current of nitrogen (obtained by connecting a T-piece to the drying apparatus) is passed in at *e*, and *A* and *C* are removed. Tube *B* is then sealed in the same way as described for *A*.

"In this way, a fairly concentrated, stable solution of phenyl biphenylyl ketone potassium is obtained. If it is desired to isolate the metal ketyl in the solid state, the procedure is as above, except that 2 g. of ketone and 2 g. of potassium are used with the same quantity of ether, and the vessel is shaken for one hour only. A supersaturated solution of the metal ketyl is thus obtained, which, after filtering into vessel *B*, will usually crystallize in the course of a few days.

"The isolation and drying of the various substances is carried out in the same way as for the triarylmethyls (*Schlenk, Weickel*, Ann. **372**, 1). A slight change in the filtering apparatus is necessary, and the apparatus is shown in Fig. 4.

"It consists of two small glass bell jars, *G* and G_1, which fit over each other, and between which is a porcelain filter plate and a filter paper. A rubber ring holds the two parts together. The method of using the apparatus is obvious from the diagram. The side tube, *H*, is filled with nitrogen and prevents air from reaching the under side of the filter paper during the filtration (*i.e.*, when no nitrogen can actually circulate through the apparatus).

"The use of two rubber balls, as shown in the figure, is also very convenient. It is possible in this way to press the mother liquor out of the precipitate on the filter without allowing the entry of air, as would occur if a filter pump were used.

"In general, the isolation and drying of the substance is carried out as for the triarylmethyls."

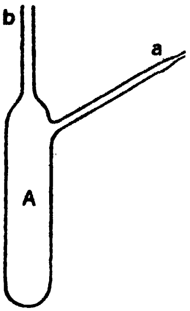


Figure 1

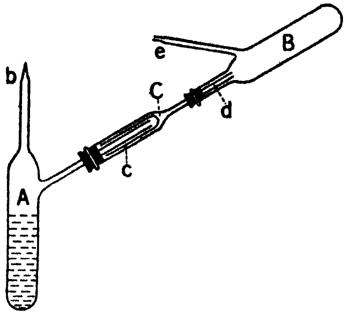


Figure 2

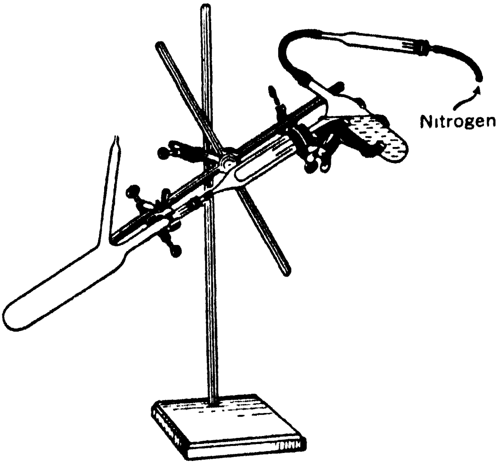


Figure 3

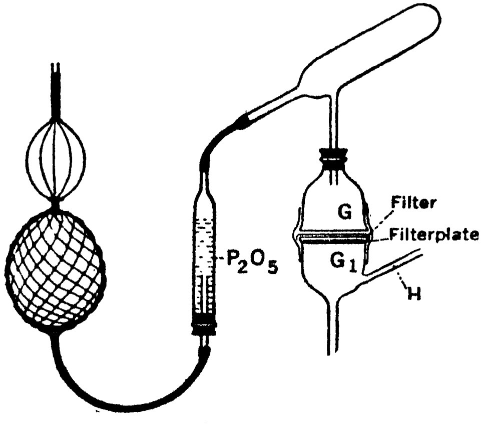


Figure 4

PROPERTIES. The metal ketyls are highly colored compounds. Their color changes considerably according to the type of ketone from which they are derived. The effect of the metal on the color has not been investigated, but it does have an effect on the solubility. For the formation of ketyls only those ketones which do not enolize can be used, and the carbonyl group must be linked with aromatic or unsaturated groups. The metal ketyls exist in equilibrium with the pinacolates (*cf.* methods of formation *3* and *4*). They are usually not sufficiently soluble for the determination of degree of dissociation. According to ebullioscopic determinations (*Schlenk*, Ber. **46**, 2840), phenyl biphenylyl ketone potassium is practically monomolecular in ether solution (*cf.* on the other hand, *Doescher*, Am. **56**, 2011; and *Bachmann*, Am. **55**, 1179, 2827; *Sugden*, Trans.Faraday Soc. **30**, 18). *Beer's* law appears to be inaccurate for solutions of iodomagnesium ketyls and iodomagnesium pinacolates (*Gomberg*, Am. **51**, 2229).

Metal ketyls with anomalous formulas. Many ketones, *e.g.*, chromone and xanthone, form anomalously constituted ketyls, in which there is only one atom of potassium and two molecules of the ketone (*Schlenk*, Ber. **46**, 2848). They can be regarded as quinhydrone-like molecular compounds between the ketyl and the ketone, or according to *Pfeiffer* (Org.Molekülverb., 1st ed., p. 66) as compounds in which one potassium atom is linked with two ketone molecules by subsidiary valencies ($Ar_2C{=}O \ldots K \ldots O{=}CAr_2$). Many diketones behave in a similar way, taking up only one atom of potassium, which is linked to two carbonyl groups. According to *Pfeiffer* (Ber. **56**, 929) such compounds can also be represented by a quinhydrone type of formula (*Staudinger*, Helv. **5**, 703). For the view that the bluish violet to blue barium and alkali metal salts of alloxantins, hydrindantin, and isatide are metal ketyls, see *Hantzsch*, Ber. **54**, 1267; a somewhat modified view of the constitution of these compounds is given by *Weitz*, Z.Elektrochem. **34**, 543.

Tautomerism of the diketyls. *Schlenk* assumed, as far back as 1911 (Ber. **44**, 1189), that a diketyl form existed in equilibrium with the normal form, and this formed the basis of the idea of tautomerism for the explanation of the experimental facts. More recently benzil dipotassium has been formulated as an enediolate (*Staudinger*, Helv. **5**, 703), and the analogous iodomagnesium compounds have been assumed to exist in the forms of enediolate and diradical in tautomeric equilibrium (*Gomberg*, Am. **51**, 2238).

CHEMICAL PROPERTIES. The metal ketyls are even more reactive than the triarylmethyls. Like the latter, they are acted upon by oxygen, but differ in the fact that they are also acted on by water and carbon dioxide. In this respect they resemble the alkali alkyls and the Grignard reagents. The halogen magnesium ketyls particularly resemble the latter.

Various reagents remove the metal atom of the ketyl, and the ketone is re-formed:

1. **Oxygen reacts in this way with the metal ketyls:**

$$2\,Ar_2\underset{\cdot}{C}{-}ONa + O_2 \rightleftharpoons 2\,Ar_2C{=}O + Na_2O_2$$

It is possible that very unstable intermediate products are formed in this reaction as is the case with the triarylmethyl peroxides. In the dry state many metal ketyls are pyrophoric when exposed to air.

2. **Iodine** reacts in a similar way with the metal ketyls:

$$2\,Ar_2\underset{\cdot}{C}{-}ONa \; + \; I_2 \;\rightleftharpoons\; 2Ar_2C{=}O \; + \; 2\,NaI$$

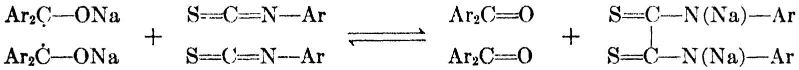
(*Schlenk*, Ber. **44,** 1184).

It is possible that in this reaction the first step is the addition of iodine to the trivalent carbon atom, followed by the splitting off of sodium iodide.

3. **Triphenylmethyl chloride** reacts like the halogens on the metal ketyls, both the alkali halide and triphenylmethyl being also formed (*Schlenk*, Ber. **46,** 2854):

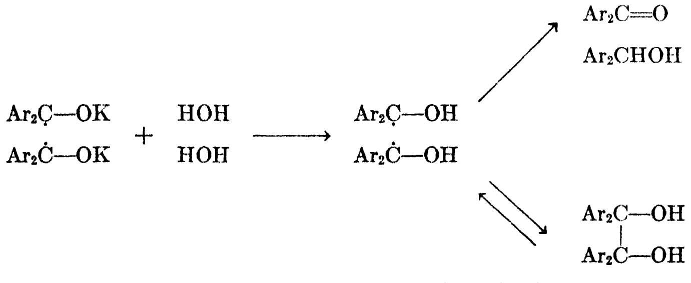
$$Ar_2\underset{\cdot}{C}{-}OK + Cl{-}CAr_3 \;\rightleftharpoons\; Ar_2C{=}O \; + \; KCl \; + \; {-}CAr_3$$

4. **Phenylthiocyanate** removes the metal atom from ketyls (*Schlenk*, Ann. **464,** 25):



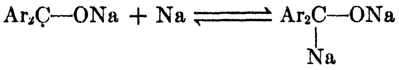
$$\begin{matrix} Ar_2\underset{\cdot}{C}{-}ONa \\ Ar_2\dot{C}{-}ONa \end{matrix} + \begin{matrix} S{=}C{=}N{-}Ar \\ S{=}C{=}N{-}Ar \end{matrix} \;\rightleftharpoons\; \begin{matrix} Ar_2C{=}O \\ Ar_2C{=}O \end{matrix} + \begin{matrix} S{=}C{-}N(Na){-}Ar \\ | \\ S{=}C{-}N(Na){-}Ar \end{matrix}$$

5. **Water** may react initially with the metal ketyls in the same way as with metal alkyls, *i.e.*, replacing the metal atom by an atom of hydrogen. The alcohol thus formed contains trivalent carbon and is very unstable, and splits up immediately into the diaryl ketone and the diarylmethanol. Pinacones can also be produced, when the aryl groups attached to the trivalent carbon atom of the alcohol do not suppress its powers of association altogether (*Schlenk*, Ber. **44,** 1187):



$$\begin{matrix} Ar_2\underset{\cdot}{C}{-}OK \\ Ar_2\dot{C}{-}OK \end{matrix} + \begin{matrix} HOH \\ HOH \end{matrix} \longrightarrow \begin{matrix} Ar_2\underset{\cdot}{C}{-}OH \\ Ar_2\dot{C}{-}OH \end{matrix} \begin{matrix} \nearrow \begin{matrix} Ar_2C{=}O \\ Ar_2CHOH \end{matrix} \\ \\ \rightleftharpoons \begin{matrix} Ar_2C{-}OH \\ | \\ Ar_2C{-}OH \end{matrix} \end{matrix}$$

6. **Sodium** and **potassium** add on to the trivalent carbon fairly vigorously (as in the case of the triarylmethyls) (*Schlenk*, Ber. **47,** 486):

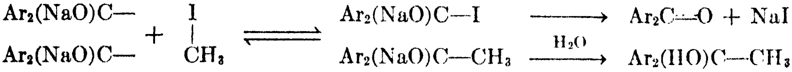


$$Ar_2\underset{\cdot}{C}{-}ONa + Na \;\rightleftharpoons\; \begin{matrix} Ar_2C{-}ONa \\ | \\ Na \end{matrix}$$

For the anomalous action of sodium on 2,3-diphenylindone sodium (only formed ntermediately), see *Schlenk*, Ann. **464,** 22.

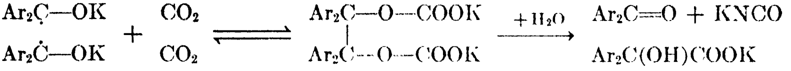
The alkylammonium radicals dissolved in liquid ammonia, react in a similar way to the alkali metals. See also p. 427.

7. **Methyl iodide** converts the ketyls into the original ketones. If water is present diarylmethylmethanols are also obtained. The reaction begins, very likely, with addition to the trivalent carbon atom. The probable course of the reaction is shown in the following scheme (*Schlenk*, Ber. **44**, 1187):



$$\begin{array}{l} Ar_2(NaO)C— \\ Ar_2(NaO)C— \end{array} + \begin{array}{c} I \\ | \\ CH_3 \end{array} \rightleftharpoons \begin{array}{l} Ar_2(NaO)C—I \\ Ar_2(NaO)C—CH_3 \end{array} \begin{array}{l} \longrightarrow Ar_2C{=}O + NaI \\ \xrightarrow{H_2O} Ar_2(HO)C—CH_3 \end{array}$$

8. **Carbon dioxide** reacts in the first place on metal ketyls in the same way as it does on phenolates in *Kolbe's* reaction, forming an ester salt of carbonic acid, which leads to association at the trivalent carbon atom. By the subsequent action of water the primary product decomposes and the original ketone, a salt of a diarylglycolic acid, and a bicarbonate are formed (*Schlenk*, Ber. **47**, 489):



$$\begin{array}{l} Ar_2\dot{C}—OK \\ Ar_2\dot{C}—OK \end{array} + \begin{array}{l} CO_2 \\ CO_2 \end{array} \rightleftharpoons \begin{array}{l} Ar_2C—O—COOK \\ \quad | \\ Ar_2C—O—COOK \end{array} \xrightarrow{+H_2O} \begin{array}{l} Ar_2C{=}O + KNCO \\ Ar_2C(OH)COOK \end{array}$$

9. **Mercury** does not act on the metal ketyls (*Schlenk*, Ann. **464**, 25).

The colors and compositions of the typical and well-known metal ketyls are shown in the accompanying table.

METAL KETYLS

Na or K compound of	Ratio of CO groups : metal atoms	Color
Diphenyl ketone[1]	1:1	Dark blue
Phenyl biphenylyl ketone[2]	1:1	Bluish green
Dibiphenylyl ketone[2]	1:1	Yellowish green
Phenyl α-naphthyl ketone[3]	1:1	Green
β-Benzpinacoline[4]	1:1	Deep red
α,α′-Dimethyl-γ-pyrone[4]	1:1	Scarlet
Chromone[4]	2:1	Orange-red
Xanthone[4]	2:1	Deep blue
O-Methylisatin[4]	1:1	Deep violet
N-Methylisatin[4]	2:1	Deep blue
Phthalophenone[4]	1:1	Dark red
m-Dibenzoylbenzene[4]	2:1	Dark red
p-Dibenzoylbenzene[4]	2:2	Deep red
Benzil (+1 K)[4]	2:1	Violet-red
Benzil (+ 2 K)[5]	2:2	Deep red
Furil[4]	2:1	Blue-black
Phenanthraquinone[4]	2:1	Dark brown

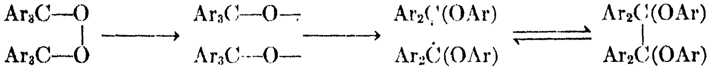
[1] *Beckmann*, Ann. **266**, 6; *Schlenk*, Ber. **47**, 486. [2] *Schlenk*, Ber. **47**, 486. [3] *Beckmann*, Ann. **266**, 10. [4] *Schlenk*, Ber. **46**, 2848–2851. [5] *Staudinger*, Helv. **5**, 703.

For the action of potassium on *p*-quinone, *o*-quinone, and diphenylketene, see *Schlenk*, Ber. **46**, 2851.

Analogous compounds are obtained from ketones and tetraalkylammonium radicals (see p. 428).

2. Diphenylphenoxymethyl

This radical, which bears the same relation to the metal ketyls as an ether to an alcoholate, is formed, according to *Wieland* (Ber. **44**, 2550), intermediately in the transformation of triphenylmethyl peroxide to the diphenyl ether of benzpinacone (in boiling xylene). The reaction probably takes place as follows:

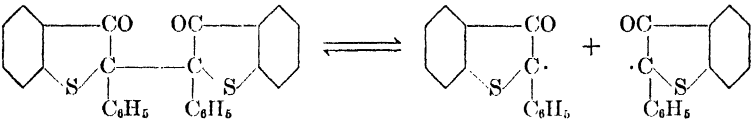


$$\begin{array}{l}Ar_3C{-}O\\ \quad\;|\\ Ar_3C{-}O\end{array} \longrightarrow \begin{array}{l}Ar_3C{-}O{-}\\ \\ Ar_3C{-}O{-}\end{array} \longrightarrow \begin{array}{l}Ar_2\dot{C}(OAr)\\ \\ Ar_2\dot{C}(OAr)\end{array} \rightleftharpoons \begin{array}{l}Ar_2C(OAr)\\ \quad\;|\\ Ar_2C(OAr)\end{array}$$

The reaction is accompanied by the development of an orange-red color, which can be observed when diphenylbenzpinacone is heated alone or in solution (m.p. 215° under CO_2). Benzene solutions of the ether mentioned are acted upon by bromine and atmospheric oxygen, particularly when warmed.

3. 2,2'-Diphenylthioindigo White

This compound, according to *Kalb* and *Bayer* (Ber. **46**, 3881), decomposes on heating in high-boiling solvents into two equal parts containing a trivalent carbon atom, which, in addition to the phenyl group, also carries a mercapto and a benzoyl radical (with a common benzene nucleus).



2,2'-Diphenylthioindigo white deepens in color when heated in solution, from pale yellow to emerald green, the reverse change taking place on cooling. The color of the solution also intensifies on dilution, contrary to Beer's law. At higher temperatures the dissolved compound is acted upon by bromine and oxygen (when passed through the solution).

4. Wurster's Dye

This compound possibly contains trivalent carbon (p. 392); for another view, see p. 425.

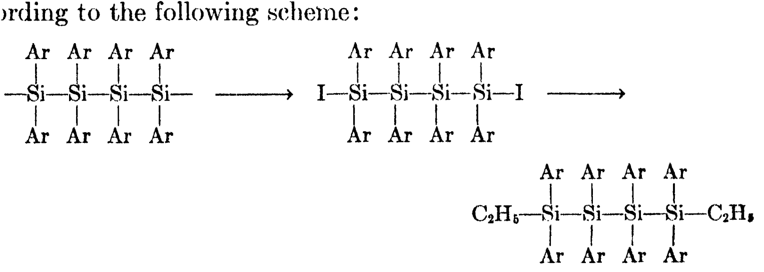
II. RADICALS WITH DI- AND MONOVALENT CARBON

Among the compounds of divalent carbon, **carbon monoxide** and its derivatives, **the isonitriles** and **fulminates**, have been known for a long time. They were regarded as $\overset{II}{C}{=}O$, $\overset{II}{C}{=}N{-}R$, $\overset{II}{C}{=}N{-}O{-}\overset{I}{Me}$. In more recent times, however, doubts have been expressed about the validity of these formulas. Thus, *Hückel* (Theor.Grundlagen org. Chem., 2nd ed., Vol. I, p. 109) states the view that in carbon monoxide the usual conception of valence does not apply. On the other hand formulas have been proposed for these compounds, and experimentally confirmed, in which, in place of the double bond, three covalences and an electrovalence are substituted (*Lindemann*, Ber. **63**, 1650): $\overset{-}{C}{\equiv}\overset{+}{O}$, $\overset{-}{C}{\equiv}\overset{+}{N}{-}R$, $\overset{-}{C}{\equiv}\overset{+}{N}{-}O{-}\overset{I}{Me}$. It is clear that these compounds do not behave like radicals. The readiness with which addition takes place at the carbon atom does not agree with the formally possible formulation with tetravalent carbon: $C{\equiv}O$, $C{\equiv}N{-}R$, $C{\equiv}N{-}O\overset{I}{-}Me$. This latter view, also, does not agree with the existence of diethoxymethylene, $C(OC_2H_5)_2$, which has been described by *Scheibler*, but the existence of which is doubted on several grounds (*Hückel, op. cit.* Vol. I, p. 111). *Schlenk* and *Bergmann* (Ann. **463,** 228) have obtained an addition product from tetraphenylallene and sodium, which they write with divalent carbon, $(C_6H_5)_2NaC{-}\overset{\cdot}{\underset{\cdot}{C}}{-}CNa(C_6H_5)_2$, because of its reactions. The preparation of $:CH_2$ by the decomposition of methane at a red-hot platinum wire, described by *Belchetz* (Trans.Faraday Soc. **30,** 170) should also be mentioned, though it does not agree with the experiments of *Rice* on the thermal decomposition of methane to $\cdot CH_3 + H$ (see *Fraser*, Trans.Faraday Soc. **30,** 182). According to *Fujio* (Bull.Chem.Soc.Japan, **5,** 249) and also *Willey* (Trans.Faraday Soc. **30,** 230) the compound $\vdots CH$, a radical with monovalent carbon, is obtained by the action of the electric discharge on methane.

III. RADICALS OF OTHER ELEMENTS OF THE FOURTH VERTICAL SERIES OF THE PERIODIC SYSTEM

(a) Silicon

The stability of **hexaphenylsilicoethane** (colorless, m.p. about 354°) in boiling xylene toward oxygen (passed through) shows that the "total valence of the silicon atom is greater than that of the carbon atom" (*Schlenk,* Ber. **44,** 1178). The reactions of the unsaturated silicon-hydrocarbon, $Si_4(C_6H_5)_8$ (colorless, m.p. about 335°) (*Kipping,* J. **125,** 2590, 2598), make it probable, however, that silicon can exist in the trivalent form. The diiodide of this compound reacts with ethylmagnesium bromide giving **octaphenyldiethylsilicotetrane,** according to the following scheme:



$$-\underset{Ar}{\overset{Ar}{Si}}-\underset{Ar}{\overset{Ar}{Si}}-\underset{Ar}{\overset{Ar}{Si}}-\underset{Ar}{\overset{Ar}{Si}}- \longrightarrow I-\underset{Ar}{\overset{Ar}{Si}}-\underset{Ar}{\overset{Ar}{Si}}-\underset{Ar}{\overset{Ar}{Si}}-\underset{Ar}{\overset{Ar}{Si}}-I \longrightarrow C_2H_5-\underset{Ar}{\overset{Ar}{Si}}-\underset{Ar}{\overset{Ar}{Si}}-\underset{Ar}{\overset{Ar}{Si}}-\underset{Ar}{\overset{Ar}{Si}}-C_2H_5$$

(b) Tin

A number of contradictory statements have been made about the dissociation of **hexaalkyldistannanes,** $R_3Sn\cdot SnR_3$, (colorless liquids, or low melting solids) (*Graebe,* Ann.suppl. **8,** 64; Ann. **364,** 51; *Grüttner,* Ber. **50,** 1808; *Krause,* Am. **47,** 2361). According to the last-mentioned work, hexamethyldistannane is dissociated in benzene at 80.5°, in concentrated solutions. The properties of **hexaaryldistannanes** (colorless, crystalline substances) are similar (*Krause*, Ber. **53,** 173; *Böeseken*, Rec. **42,** 1017). For an explanation of this see *Walden*, Chem.der fr.Rad., pp. 250, 341. The capacity of these compounds to pass into the tin trialkyls and tin triaryls, compounds with trivalent tin, has been definitely proved. The dissociation of **hexacyclohexyldistannane** has been proved (*Krause*, Ber. **57,** 532). It is noteworthy that the tin diaryls (but not the tin dialkyls) are colored (orange-yellow powders). See also Vol. III, p. 172.

(c) Lead

The (yellow) compounds of lead with three aromatic, alicyclic, or aliphatic radicals occur in sufficiently dilute solution in benzene in the monomolecular state (*Krause*, Ber. **55,** 888; *Midgley*, Am. **45,** 1821). It should be noted that lead diaryls (intensely red) readily pass into lead triaryls when gently warmed with excess of aryl magnesium bromides. The ready transformation of triphenyl lead into tetraphenyl lead on heating, according to the equation:

$$4\,(C_6H_5)_3Pb = 3\,(C_6H_5)_4Pb + Pb$$

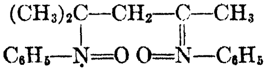
takes place with greater difficulty with tri-*p*-tolyl lead, and does not occur at all for tri-*o*-tolyl and tri-*p*-xylyl lead. See also Vol. III, p. 173.

IV. ORGANIC RADICALS WITH TETRAVALENT NITROGEN

Piloty's porphyrexide (Ber. **34,** 1884, 2354; **36,** 1283), of which the constitution is not yet definitely known, appears to be the first organic radical of tetravalent nitrogen to be discovered. The chemistry of the organic compounds of tetravalent nitrogen was, however, started by *Wieland* (Ber. **47,** 2111) by his discovery of **diarylnitric oxides,** $Ar_2N{:}O$. The analogy between the equilibria:

$$2\,Ar_3C\cdot \rightleftharpoons Ar_3C—CAr_3 \quad \text{and} \quad 2\,\cdot NO_2 \rightleftharpoons O_2N—NO_2$$

led to the investigation of organic derivatives of nitrogen dioxide (*Wieland*, Ber. **42,** 3029). A compound which is formulated as a diarylaminoaryl-nitric oxide, $(Ar_2N—)(Ar—)N{=}O$, is probably related, constitutionally, to the diarylnitric oxides (*Goldschmidt*, Ber. **55,** 633). An analogous compound to the diarylnitric oxides is also formed by dehydrogenation of the condensation product of β-phenylhydroxylamine and acetone. It is given the formula (*Banfield*, J. **1926, 1612**):



$$\begin{array}{l}(CH_3)_2C—CH_2—C—CH_3 \\ \quad\;\;\, | \qquad\qquad\;\; \| \\ C_6H_5—\dot{N}{=}O \;\; O{=}N—C_6H_5\end{array}$$

Another class of organic compounds with tetravalent nitrogen comprises the **tetraalkylammonium radicals,** so far only obtained in solution or as amalgams. These have been investigated chiefly by *Schlubach* (Ber. **54,** 2811). The **dipyridinium radicals,** investigated by *Weitz* (Ber. **57,** 153), are closely related to these substances, being diradicals of the ammonium type. Possibly the subhalides (Ber. **59,** 432) and Wurster's dye, $[R_2\underset{\cdot}{N}{=}C_6H_4{=}\overset{+}{N}R_2]Br$ (or formulated according to *Weitz*, Z.Elektrochem. **34,** 542) also belong to this class. The **aminium** and **hydrazinium salts,** discovered by *Weitz* (Ber. **59,** 2307; **60,** 1203), should also be mentioned.

(a) Diarylnitric Oxides, Diarylnitroxides

The deep-red, crystalline diarylnitric oxides resemble in many respects nitrogen dioxide, from which they may be supposed to be derived by the replacement of an oxygen atom by two aryl radicals. They differ from their inorganic analogue, however, in that they do not associate at low temperatures, but it may be assumed that this is only a difference of degree.

METHODS OF FORMATION. *1.* The method which led to the discovery of the diarylnitric oxides depends on the dehydrogenation of diarylhydroxylamines, which can be obtained from the nitroso compounds of the aromatic series and arylmagnesium halides (*Wieland,* Ber. **47,** 2111; see also Ber. **48,** 1117):

$$Ar{-}N{=}O + ArMgBr \rightleftharpoons Ar_2N{-}O{-}MgBr$$

$$Ar_2N{-}O{-}MgBr + H_2O \rightleftharpoons ArN{-}OH + HOMgBr$$

$$2\,Ar_2N{-}OH + Ag_2O \rightleftharpoons 2\,Ar_2\underset{\cdot}{N}{=}O + H_2O + 2\,Ag$$

2. In contrast to the above oxidation method, is the method of reducing suitable derivatives of nitric acid (*Meyer,* Ber. **52,** 1476; **54,** 327). The starting substance is the (not isolated) condensation product (I) of nitric acid with a phenol ether, which reacts like a base toward perchloric acid. Apparently an oxonium salt (II) is formed. This perchlorate can be reduced with zinc dust to the diarylnitric oxide:

$$2\,RO{-}C_6H_4{-}H + O{=}NO_2H - H_2O \rightleftharpoons (p\text{-}RO{-}C_6H_4)_2NOOH \quad (I)$$

$$(RO{-}C_6H_4)_2NOOH + HClO_4 - H_2O \rightleftharpoons [RO{-}C_6H_4{-}N({=}O){=}C_6H_4{=}\overset{+}{O}R]\overset{-}{C}lO_4 \quad (II)$$

$$[RO{-}C_6H_4{-}N({=}O){=}C_6H_4{=}\overset{+}{O}R]\overset{-}{C}lO_4 + {}^1/_2\,Zn \rightleftharpoons (p\text{-}RO{-}C_6H_4)_2\underset{\cdot}{N}{=}O + \frac{Zn}{2}\,ClO_4$$

PROPERTIES. The diarylnitric oxides are highly colored compounds. Diphenylnitric oxide forms crystals resembling chromic acid, and the fiery color of its solutions resembles that of nitrogen dioxide vapor, but is deeper red. The band spectrum of diphenylnitric oxide resembles that of nitrogen dioxide. The effect which the nature of the aryl group attached to the nitrogen has on the stability of the diarylnitric oxide is very remarkable, as shown in the following table (*Wieland,* Ber. **53,** 216):

Di-*p*-tolylnitric oxide, can be kept for about 3 hours.
Diphenylnitric oxide, can be kept for about 24 hours.
p,p'-Dinitrodiphenylnitric oxide, can be kept for about a month.
Dianisylnitric oxide, can be kept for about a year.

The above compounds melt with decomp. at 59–60°, 64°, 109°, and 150°, respectively.

For the determination of the paramagnetic susceptibility of diarylnitric oxides, see *Cambi*, Gazz. **63**, 579; *Galavics*, Helv.Physica Acta, **6**, 555; *Katz*, Z.Physik, **87**, 238.

CHEMICAL PROPERTIES. The diarylnitric oxides are exceedingly reactive compounds. Very probably the reagents first attack the free valence of the nitrogen, and there are subsequently further changes which often lead to substances far removed from the starting material (*Wieland*, Ber. **47**, 2111; **53**, 210). Their reactions with other radicals are of particular interest:

1. **Triphenylmethyl** reacts comparatively simply with *bis*-(*p*-nitrophenyl)-nitric oxide, both radicals adding to each other. The triphenylmethyl adds on to the oxygen, since the reaction product gives *p,p'*-diaminodiphenylamine and triphenylmethanol on reduction:

$$(O_2N{-}C_6H_4)_2\underset{\cdot}{N}O + \cdot C(C_6H_5)_3 \rightleftharpoons (O_2N{-}C_6H_4)_2N{-}O{-}C(C_6H_5)_3$$

In the case of diphenylnitric oxide itself, the *Tschitschibabin* transformation (see p. 399) comes into the reaction (*Wieland*, Ber. **53**, 214).

2. **Nitric oxide** reacts initially on diphenylnitric oxide as it does with its inorganic analogue ($\underset{\cdot}{N}O + \underset{\cdot}{N}O_2 = N_2O_3$). The primary addition product, $(C_6H_5)_2N({=}O){-}N{=}O$, however, isomerizes to *p*-nitrodiphenylamine, apparently through the formerly unobtained isomer diphenylnitramide:

$$(C_6H_5)_2N({=}O){-}N{=}O \longrightarrow (C_6H_5)_2N{-}NO_2 \longrightarrow (O_2N{-}C_6H_4)(C_6H_5)NH$$

The latter then undergoes a nitrosation by reaction with the primary addition product:

$$(O_2N{-}C_6H_4)(C_6H_5)NH + (C_6H_5)_2N({=}O){-}N{=}O \longrightarrow (O_2N{-}C_6H_4)(C_6H_5)N{-}NO + (C_6H_5)_2N{-}OH$$

The chief product of the reaction is *p*-nitrodiphenyl-nitrosamine.

3. **Nitrogen dioxide** reacts with diphenylnitric oxide with formation of *bis*-(*p*-nitrophenyl)-nitric oxide. The reaction appears to take place according to the following scheme:

$$(C_6H_5)_2\underset{\cdot}{N}{=}O + \underset{\cdot}{N}O_2 \rightarrow (C_6H_5)_2N({=}O){-}NO_2 \rightarrow (O_2N{-}C_6H_4)C_6H_5N{-}OH \xrightarrow{\text{oxid. }(NO_2)} (O_2N{-}C_6H_4)(C_6H_5)\underset{\cdot}{N}{=}O$$

$$(O_2N{-}C_6H_4)(C_6H_5)\underset{\cdot}{N}{=}O + \underset{\cdot}{N}O_2 \rightarrow (O_2N{-}C_6H_4)(C_6H_5)N({=}O){-}NO_2 \longrightarrow (O_2N{-}C_6H_4)_2N{-}OH \xrightarrow{\text{oxid. }(NO_2)} (O_2N{-}C_6H_4)_2\underset{\cdot}{N}{=}O$$

By various other reactions the diarylnitric oxides give diarylamines (which are often stages in further transformations). The majority of reducing agents react in this way.

4. **Hydriodic acid** (acidified dilute KI solution) reacts quantitatively with diphenylnitric oxide according to the equation:

$$(C_6H_5)_2N{=}O + 3\,HI \rightleftharpoons (C_6H_5)_2N{-}H + H_2O + 3\,I$$

5. **Dilute mineral acids** cause catalytic disproportionation of diphenylnitric oxide to diphenylamine and quinoneanil oxide (*Wieland*, Ber. **53,** 215; see also *Meyer*, Ber. **54,** 328):

$$(C_6H_5)_2N{=}O + H{-}C_6H_4{-}N({=}O)C_6H_5 \rightleftharpoons (C_6H_5)_2N{-}H + O{=}C_6H_4{=}N({=}O)C_6H_5$$

Diphenylnitric oxide undergoes the same decomposition (in ether solution) very often without known cause.

6. **Concentrated sulfuric acid** gives a deep blue solution with diphenylnitric oxide.

7. **Bromine** converts diphenylnitric oxide into 2,4,2′,4′-tetrabromodiphenylamine (*Wieland*, Ber. **47,** 2112; *Meyer*, Ber. **54,** 329).

8. **Phenylhydrazine** reduces diarylnitric oxides only to the diarylhydroxylamine stage, *e.g.:*

$$(p\text{-}NO_2{-}C_6H_4)_2N{=}O \xrightarrow{C_6H_5NH{-}NH_2} (p\text{-}NO_2{-}C_6H_4)_2N{-}OH$$

Diarylnitric oxides, other than those described above, see *Meyer*, Ber. **54,** 333. **2,6,2′,6′-Tetramethyl-4,4′-dimethoxydiphenylnitric oxide,** m.p. 163°. **2,2′-Dimethyl-4,6,4′,6′-tetramethoxydiphenylnitric oxide,** m.p. 175° (dec.). **2,4,6,2′,4′,6′-Hexamethoxydiphenylnitric oxide,** m.p. 194° (dec.). As distinct from diphenylnitric oxide, these compounds are very stable and show no band spectrum in solution.

(b) Organic Substituted Ammonium Radicals

1. *Alkylammonium Radicals*

Alkylammonium radicals have so far only been obtained in the form of blue solutions in liquid ammonia, or as amalgams. It is only the quaternary alkylammonium radicals that have any real stability, in analogy with the greater electrolytic dissociation of their salts in aqueous solution, and the stability of the alkylated ammonium hydroxides. The effect of arylation on the stability of the methyls should also be mentioned (*Schlubach*, Ber. **56,** 1892). Finally, the similarity between tritylsodium and trityltetramethylammonium is noteworthy (Ber. **49,** 605).

METHODS OF FORMATION. *1.* By electrolysis of alkylammonium salts in liquid ammonia (*Palmaer*, Z.Elektrochem. **8,** 729), best at −78° and using tetraalkylammonium iodides (*Schlubach*, Ber. **53,** 1689; **54,** 2811, where other details of technique are given).

1a. By electrolysis of alkylammonium salts using a mercury cathode, when alkylammonium amalgams are obtained. Alcohol is usually used as a solvent (*McCoy*, Am. **33,** 273; J.Phys.Chem. **16,** 261).

2. By acting on alkylammonium halides with alkali metals in liquid ammonia (*Schlubach*, Ber. **54**, 2814):

$$N(C_2H_5)_4Cl + K \rightleftharpoons \cdot N(C_2H_5)_4 + KCl$$

PROPERTIES. The blue solutions of tetraalkylammonium radicals in liquid ammonia resemble in color exactly the solution of sodium in ammonia. When cooled to −78°, the color of the solution slowly fades after some hours, which *Schlubach* (Ber. **54**, 2813) ascribes to dimerization of the radical, since the decolorized solution gives the same reactions as the blue solutions. The amalgams of tetraalkylammonium radicals resemble very much in appearance sodium amalgam.

Comparison of Addition Products of Tetraethylammonium and Alkali Metal

(Ber. **56**, 1891)

Type	Compound	With tetraethylammonium	With alkali metals	State
$>C=O$	Benzophenone	Blue	Blue	Solution
	Phenyl biphenylyl ketone	Yellow	Mono: yellow to deep green; Di: deep blue	Solution
	Dimethylpyrone	Yellow, solid	Brick red	Solid
		Brick red	Violet to deep red	Solution
	β-Benzpinacoline	Brick red	Violet to deep red	Solution
$-\overset{O}{\overset{\|}{C}}-\overset{O}{\overset{\|}{C}}-$	Benzil[a]	1. Yellow 2. Green	Violet	Solid
	Phenanthraquinone[a]	1. Yellowish brown 2. Magenta	Dark brown	Solid
$>C=C<$	Anthracene	Yellowish green, brown flocks	Bluish violet	Solution
	Stilbene	Reddish brown	Brownish violet	Solid
	Tetraphenylethylene	Reddish violet, solid	Dark red	Solution
$>C=N-$	Benzalaniline	Bright yellow Wine red	Bright yellow	Solution
$-N=N-$	Azobenzene	Dark reddish brown	Dark violet	Solid
$-C\equiv C-$	Tolane[a]	1. Greenish black 2. Flesh colored	......	Solid
$-C\equiv N$	Tolunitrile	Dark brown	......	Solid

[a] In the action of tetraethylammonium on benzil, phenanthraquinone, and tolane, the color stages 1 and 2 occur one after the other. The color of the mono-alkali metal compound of phenyl biphenylyl ketone is not as indicated in the above table, which is the original table, but is bluish green (Ber. **47**, 486). A sensitive test for alkylammonium radicals depends on the easy formation of an addition product with dimethylpyrone.

CHEMICAL PROPERTIES of the radicals dissolved in liquid ammonia: *1.* **Thermal decomposition.** Even at the boiling point of liquid ammonia (−33.5°) the tetraalkylammonium radicals tend to break down:

$$2\,N(C_2H_5)_4 \rightleftharpoons 2\,N(C_2H_5)_3 + (C_2H_5)_2$$

2. **Iodine** is taken up by tetraalkylammonium radicals with formation of the iodide.

3. **Oxygen** has no action.

4. **Sulfur** is taken up with formation of sulfides.

5. **Unsaturated compounds,** which are able to add on to alkali metals, also add on to tetraalkylammonium radicals dissolved in liquid ammonia. The adducts are in each case very similar to each other, as the table on p. 428 shows (*Schlubach*, Ber. **56**, 1891).

CHEMICAL PROPERTIES OF THE RADICAL AMALGAMS. Tetramethylammonium amalgam can be kept for about a day below 10°. It is more reactive than sodium amalgam. The electrode potential of tetramethylammonium amalgam is about 0.6 volt higher than that of ammonium amalgam.

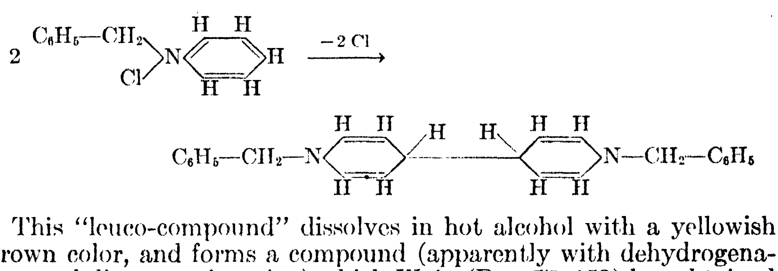
1. **Copper and tin salt solutions** are immediately reduced by tetramethylammonium amalgam to the metal.

2. **Salts of sodium, potassium,** and **ammonium** react with tetramethylammonium amalgam with formation of sodium, potassium, and ammonium amalgam, respectively.

*2. Dipyridinium Radicals**

It is possible to explain the behavior of many N,N′-disubstituted dihydro-γ,γ′-dipyridyls on the assumption of tautomerism. Whether this is justified is doubtful.

Hofmann (Ber. **14**, 1503) obtained **N,N′-dibenzyl-N,γ,N′,γ′-tetrahydro-γ,γ′-dipyridyl** by removing the halogen from N-benzylpyridinium chloride (*Emmert*, Ber. **52**, 1351; for another view, see *Weitz*, Ber. **57**, 153):



This "leuco-compound" dissolves in hot alcohol with a yellowish brown color, and forms a compound (apparently with dehydrogenation and disproportionation) which *Weitz* (Ber. **57**, 153) has obtained in the solid form, and regards as a dipyridinium radical (in tautomeric equilibrium with a quinoid isomer):

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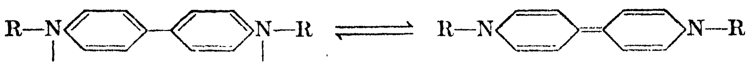
* The name dipyridonium radicals later proposed for these compounds (*Weitz*, Ber. **59**, 2307) appears to be less suitable, since it emphasizes their relationship to the pyridones, and is contrary to the almost universal name "pyridinium salts."



Emmert, Ber. **55,** 2322; **56,** 491, and *Dimroth,* Ber. **55,** 3693, admit only the quinoid formulation of this and analogous compounds.

PROPERTIES. Dipyridinium radicals are crystalline, brownish red substances, which dissolve (in an atmosphere of hydrogen) in organic solvents with a yellowish brown color (in the presence of oxygen a deep blue oxidation product is formed; see further below). The double alkylated radicals and dibenzyldipyridinium (*Weitz,* Ber. **57,** 157) and the corresponding phenylated, benzoylated (*Weitz,* Ber. **57,** 155, 162), and acetylated compounds (*Dimroth,* Ber. **55,** 1223) have so far been investigated. The benzoylated and acetylated compounds, as acid amides, have practically none of the properties of an ammonium radical, and for them the quinoid formula is to be preferred.

FORMATION. *1.* By regulated oxidation of the "leuco-compounds," *e.g.*, by disproportionation, oxygen, or iodine (see above). *2.* By reduction of the quaternary dipyridinium dihalides by hydrolysis, or by the action of zinc or magnesium in aqueous solution:

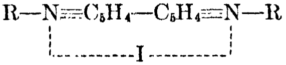
$$I{-}(R)N{\equiv}C_5H_4{-}C_5H_4{\equiv}N(R){-}I \xrightarrow{-2I} R{-}\underset{\cdot}{N}{\equiv}C_5H_4{-}C_5H_4{\equiv}\underset{\cdot}{N}{-}R$$

The reduction can also be brought about with the leuco-compound (*Weitz,* Ber. **55,** 2874).

CHEMICAL PROPERTIES. *1.* The most outstanding property of these compounds is their tendency in solution in the presence of air to pass into deep blue (when alkylated or benzylated dipyridinium radicals are used) or dark green (when phenylated compounds are used) oxidation products. This reaction occurs so quickly that for some time it was assumed that the dipyridinium radicals were blue or green. The same coloration is produced by the careful addition of **iodine,** analogous compounds being obviously formed, which have been obtained in the crystalline form (*Weitz,* Ber. **57,** 156). They have the composition of 1 mole radical:1 atom iodine. The compounds may be regarded as "semiradicals":

$$R{-}\underset{\cdot}{N}{\equiv}C_5H_4{-}C_5H_4{\equiv}N(R){-}I$$

or as subhalides:



$$R{-}N{\equiv}C_5H_4{-}C_5H_4{\equiv}N{-}R \quad (\ldots I \ldots)$$

(*Weitz,* Ber. **59,** 432), or as dimeric quinhydrones (*Emmert,* Ber. **55,** 2322; **56,** 491; **57,** 1792; and *Dimroth,* Ber. **55,** 3693). These subhalides (similar to *Wurster's* red) may correspond to the products obtained by the action of air (OH instead of I). The further action of iodine (air) converts the above-mentioned intermediate products into quaternary dipyridinium diiodides (or dihydroxides).

2. **Carbon dioxide,** in the presence of oxidizing agents (nitric oxide or oxygen), reacts with dibenzyldipyridinium with formation of N,N′-dibenzyl-γ,γ′-dipyridinium bicarbonate, indicating the metallic character of the radical (*Weitz*, Ber. **55**, 2864). It corresponds to a noble metal, since it is displaced from its salts by zinc (method *2* of formation).

(c) Arylated Aminium and Hydrazinium Salts

1. Triarylaminium Salts

If in the triarylamines, each aryl extracts more affinity from the nitrogen than corresponds to one valence bond, these compounds must resemble ammonium radicals. Starting with this idea, *Weitz* (Z. angew.Chem. **39**, 1193; Ber. **59**, 2307; **60**, 545) has shown that the triarylamines combine with acid radicals (*e.g.*, ClO_4) to give blue "triarylaminium salts." In these salts, the cation is a radical, as the following comparison shows:

$[Ar_3\underset{\cdot}{N}]ClO_4$	$[R_3NH]ClO_4$
Aminium salt	Ammonium salt

The triarylaminium salts contain, from the formal point of view, tetravalent nitrogen. They correspond in their degree of oxidation to the diaryl nitrogen radicals (with divalent nitrogen, see p. 433) to which they stand, as far as the formula is concerned, in the same relationship as the quaternary ammonium salts to the tertiary amines. In agreement with this view, the triarylamines in general do not form salts with acids. Perchloric acid alone combines with triphenylamine to give a normal salt, $[(C_6H_5)_3NH]ClO_4$, which, however, is very readily hydrolyzed (*Hofmann*, Ber. **43**, 1080).

For the earlier known blue perbromide of the triarylamines which, however, was not regarded as an aminium salt, and to which the formula $[Ar_3\underset{\cdot}{N}]Br(Br)_2$ is now ascribed, see *Pummerer*, Ber. 59, 2309.

METHODS OF PREPARATION. *1.* From the triarylamines and the acid radicals, triarylaminium salts are obtained. Thus tri-*p*-tolylamine and chlorine tetroxide give **tritolylaminium perchlorate:**

$$x(CH_3{-}C_6H_4{-})_3N + (ClO_4)_x \rightleftharpoons x[(CH_3{-}C_6H_4{-})_3\underset{\cdot}{N}]ClO_4$$

2. Triarylamines (like noble metals) form salts with acids in the presence of an oxidizing agent. Thus, tri-*p*-tolylamine, picric acid, and lead dioxide give **tri-*p*-tolylaminium picrate,** $[(CH_3{-}C_6H_4)_3\underset{\cdot}{N}]{-}O{-}C_6H_2(NO_2)_3$.

Neither reaction can be carried out with triphenylamine because the *p*-H atom is too easily oxidized.

PROPERTIES. The blue solutions of triarylaminium salts show a band spectrum. Even quite dilute solutions of tritolylaminium perchlorate in chloroform obey Beer's law accurately, so that this compound and its analogues are salts and not (dissociating) quinhydrones (*Weitz*, Ber. **60**, 547).

CHEMICAL PROPERTIES. *1.* **Reducing agents** convert triarylaminium salts into triarylamines, *e.g.*:

$$[Ar_3\underset{\cdot}{N}]ClO_4 + HI \rightleftharpoons Ar_3N + HClO_4 + I$$

2. **Water** readily hydrolyzes the triarylaminium salts, although a triarylaminium hydroxide has not yet been obtained. These hydroxides are obviously very unstable.

3. **Quaternary γ,γ'-dipyridinium salts** are precipitated from alcoholic solutions of triarylaminium perchlorates in the form of their difficultly soluble perchlorate (this would appear to be a good reagent for the ClO_4 ion in alcoholic solution). A suitable substance for this reaction is N,N'-dibenzyl-γ,γ'-dipyridinium dichloride (*Weitz*, Ber. **60**, 546). *Cf.* p. 430.

For triarylaminium salts with an amide group in the *p*-position, and addition products with antimony pentachloride, and phosphorus pentachloride, and for the ammonium character of the diarylamines, see *Weitz*, Ber. **59**, 2311; **60**, 547, 549.

2. Tetraarylhydrazinium Salts

These compounds, which were also discovered by *Weitz* (Ber. **60**, 1203) resemble the triarylaminium salts so closely that it is only necessary to mention a few outstanding points concerning them.

The tetraarylhydrazinium salts bear the same formal relationship to the triarylhydrazyls (p. 439) as the quaternary ammonium salts do to tertiary amines.

The tetraarylhydrazinium salts are violet-colored compounds, whose solutions show a characteristic band spectrum. The composition of these radicals is represented by the formula $[Ar_2N{-}\underset{\cdot}{N}Ar_2]X$. A second acid radical cannot be taken up.

METHODS OF FORMATION. Tetraarylhydrazinium salts are obtained in the same way as the triarylaminium salts. The first method mentioned above can, however, be used with nonoxidizing acids (*e. g.*, HCl) on tetraarylhydrazines. No hydrogen is evolved in this case. The reaction is explained by the fact that, in the absence of an oxidizing agent, the tetraarylhydrazine itself acts in this capacity (in the same way as phenylhydrazine does in the formation of osazones).

$$3\,Ar_2N{-}NAr_2 + 2HCl \rightleftharpoons 2[Ar_2N{-}\underset{\cdot}{N}Ar_2]Cl + 2\,Ar_2NH$$

By the action of triarylaminium salts on tetraarylhydrazines, tetraarylhydrazinium salts are obtained (from which it follows that the tetraarylhydrazines are relatively less noble "ammonium radicals" than the triarylamines):

$$[Ar_3\underset{\cdot}{N}]X + Ar_2N{-}NAr_2 \rightleftharpoons Ar_3N + [Ar_2N{-}\underset{\cdot}{N}Ar_2]X$$

CHEMICAL PROPERTIES. Even very mild reducing agents convert tetraarylhydrazinium salts into tetraarylhydrazines. The tetraarylhydrazinium salts are thus good oxidizing agents. They liberate iodine from potassium iodide, even in neutral solution, and the hydrazine is formed:

$$[Ar_2N{-}\underset{\cdot}{N}Ar_2]X + KI \rightleftharpoons Ar_2N{-}NAr_2 + I + KX$$

(The foregoing equation shows that tetraarylhydrazinium iodide does not exist.)

V. ORGANIC RADICALS WITH DIVALENT NITROGEN

The organic radicals of divalent nitrogen so far obtained are produced by dissociation of two trivalent nitrogen atoms linked together, in consequence of the effect of the four groups attached to these atoms. In the simplest case, these substituents are aromatic radicals. We then have **tetraarylhydrazines,** which dissociate into two molecules of **diarylnitrogen:** $Ar_2N—NAr_2 \rightleftharpoons 2\ Ar_2\underset{\cdot}{N}$. To these important compounds analogous to hexaphenylethane and triphenylmethyl, discovered by *Wieland* (Ann. **381,** 200), must be added compounds obtained by replacing one of the two aryls attached to a nitrogen atom, a diarylamino-group. The **hexaaryltetrazanes** and their decomposition products, the **triarylhydrazyls:**

$$Ar_2N—N(Ar)—Ar(N)—NAr_2 \rightleftharpoons 2\,Ar_2N—\underset{\cdot}{N}Ar$$

fall into this class (*Goldschmidt,* Ber. **53,** 44). Finally, the little investigated compounds in which the dissociating nitrogen atoms are not directly linked with carbon, but with two thioaryl groups, must be mentioned. These are the **tetrathioarylhydrazines,** which break down to the **dithioaryl nitrogens** (*Lecher,* Ber. **58,** 423):

$$(ArS)_2N—N(SAr)_2 \rightleftharpoons 2\ (ArS)_2\underset{\cdot}{N}$$

The nitroso compounds, which can be regarded as diradicals with divalent nitrogen and monovalent oxygen, are dealt with under radicals with monovalent oxygen (p. 451).

(a) Diaryl Nitrogens

Literature: *Wieland,* Die Hydrazine, Enke, Stuttgart, 1913, pp. 62–81; Ber. **53,** 1336, and earlier papers.

The tetraarylhydrazines resemble the hexaarylethanes not only in their capacity to dissociate, but also in the great effect exerted on the properties of the substances by the nature of the substituents. The rather surprising fact has been discovered that the same substituents can exert an entirely different effect on the dissociation of the two types of compound. The tendency toward dissociation is smaller in the case of tetraphenylhydrazine than for hexaphenylethane. If the phenyl groups in tetraphenylhydrazine are replaced by biphenylyl radicals, or if nitro groups are introduced into the phenyl, in the first case there is a weak, and in the latter a strong, reversal of the tendency to dissociation, which is in sharp contrast to the effect of these changes on hexaarylethanes. On the other hand, the tendency of the tetraarylhydrazines to dissociate is increased by the introduction of methoxy or dimethylamino groups in the *p*-position. According to experiments so far carried out, negative substituents in the benzene nucleus bring about a decrease, and positive substituents an increase, in the tendency to dissociate. The methyl group is more effective in the *o*- than in the *p*-position (*Wieland,* Ann. **392,** 130). The order of aromatic substituents in increasing order of effect on the dissociation is as follows: p-NO_2—$C_6H_4\cdot$, p-C_6H_5—$C_6H_4\cdot$, $C_6H_5\cdot$, p-CH_3—$C_6H_4\cdot$, o-CH_3—$C_6H_4\cdot$, p-CH_3O—$C_6H_4\cdot$, p-$(CH_3)_2N$—$C_6H_4\cdot$.

METHODS OF FORMATION. *1.* Diarylamines give tetraarylhydrazines when oxidized with powdered permanganate in acetone solution at 10°, or with lead dioxide in benzene or ether. This is the most important method (*Wieland*, Ber. **39**, 1500):

$$Ar_2NH + HNAr_2 \xrightarrow{-2\,H} Ar_2N{-}NAr_2$$

2. Tetraphenylhydrazine was first obtained by the action of iodine on sodio-diphenylamine (*Chattaway*, J. **67**, 1090).

3. When diethyl- and dibenzyl-N-chloramine are acted upon by copper they give the disproportionation products (see below) of diethyl- and dibenzylnitrogen (*Wieland*, Ann. **392**, 135, 152).

4. Thermal decomposition of tetraaryltetrazenes gives tetraarylhydrazines with evolution of nitrogen (*Wieland*, Ber. **41**, 3506).

$$Ar_2N{-}N{=}N{-}NAr_2 \longrightarrow Ar_2N{-}NAr_2 + N_2$$

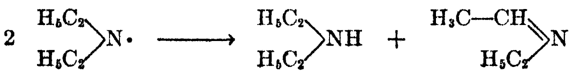
Mixed aromatic tetrazenes give the corresponding hydrazines, and, if tetraalkyltetrazenes are used, the intermediate formation of dialkylnitrogens can be demonstrated by their action on nitric oxide. (See also p. 435; *Wieland*, Ann. **392**, 135).

5. The addition product of diaryl nitrogens and nitric oxide (see below) break down at 130° into their components. At the high temperature, however, the radicals produced undergo disproportionation (*Wieland*, Ann. **381**, 211; **392**, 131).

6. The same holds for the difficultly obtainable addition products of diaryl nitrogens and triarylmethylene (*Wieland*, Ann. **381**, 214).

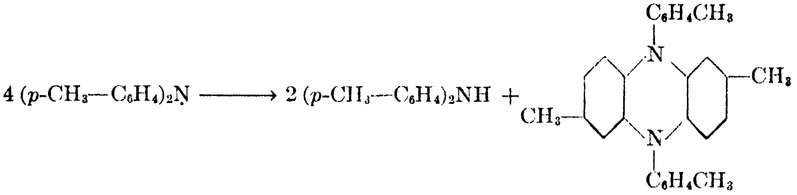
PROPERTIES. Diphenylnitrogen is emerald green in color, while di-p-tolyl- and dibiphenylylnitrogen are dark yellow. When subjected to the action of cathode rays at the temperature of liquid air, the dimer phosphoresces with a bluish glow, which ceases as soon as the rays are switched off (*Wieland*, Ann. **381**, 205). Dianisylnitrogen is bright green in benzene solution, while di-(p-dimethylaminophenyl)-nitrogen is yellow (*Wieland*, Ber. **45**, 2602; **48**, 1078). These radicals do not show typical band spectra. For solutions of the highly dissociated tetraarylhydrazines, *Beer's* law is apparently inaccurate. These radicals are very sensitive toward light and mineral acids.

CHEMICAL PROPERTIES. *1.* **Disproportionation.** The diarylnitrogens are distinguished from the triarylmethyls by their lower stability. According to *Wieland's* rule (Ann. **401**, 234) an oxidation-reduction reaction takes place, as for the hydrogen-containing radicals, but it is more marked for the dialkyl nitrogens. Thus, by thermal decomposition of tetraalkyltetrazenes (*cf.* method of formation *4*), instead of obtaining tetraalkylhydrazines, secondary amines and Schiff's bases are formed (*Wieland*, Ann. **392**, 129), *e.g.*:



$$2\,(H_5C_2)_2N\cdot \longrightarrow (H_5C_2)_2NH + H_3C{-}CH{=}N{-}C_2H_5$$

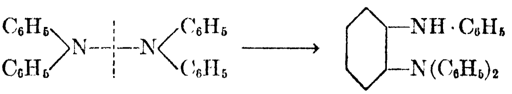
Tetraarylhydrazines give N,N′-diaryldihydrophenazines ("perazines") and secondary amines under the influence of light (*Wieland*, Ber. **41**, 3484; Ann. **381**, 202; **392**, 156), *e.g.:*



Dilution favors the decomposition. Evidently it is only the free radical that tends to disproportionate (*cf.* the analogous behavior of the triarylmethyls, p. 399).

In addition to the formation of perazine in the above reaction, indamine formation has also been observed (Ber. **53**, 1317; see also p. 436).

2. **Transformation into** *o*-**semidines.** This transformation occurs with tetraphenylhydrazine in boiling toluene to the extent of about 10%, in addition to the decomposition mentioned above (*Wieland*, Ann. **381**, 203).



This reaction predominates in the case of nascent di-β-naphthylnitrogen (*Wieland*, Ann. **392**, 131). In spite of its apparent similarity, this reaction is not connected with the semidine and benzidine transformations, but it is essentially similar to the *Tschitschibabin* transformation (p. 399).

3. **Nitric oxide** combines with diaryl nitrogens and their analogues to form the comparatively stable nitrosamines (decomposition temperature of diarylnitrosamines is about 130°):

$$Ar_2N\cdot + \cdot NO \rightleftharpoons Ar_2N{-}NO$$

This is an important method for fixing these unstable radicals (*Wieland*, Ann. **381**, 203; **392**, 142). The same is true of the following reaction:

4. **Triphenylmethyl** forms even more stable addition products with diaryl nitrogens than does nitric oxide (*Wieland*, Ann. **381**, 204; Ber. **45**, 2605):

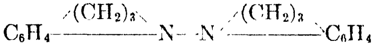
$$Ar_2N\cdot + \cdot C(C_6H_5)_3 \rightleftharpoons Ar_2N{-}C(C_6H_5)_3$$

5. **Acids** react with the tetraarylhydrazines very readily, causing hydrolytic fission at the N—N linkage. Ar_2NH and $HO{-}NAr_2$ are first formed. The diarylhydroxylamine then undergoes further reactions (*Wieland*, Ann. **381**, 200). By the action of concentrated sulfuric acid on tetraphenylhydrazine, N,N′-diphenylbenzidine, $C_6H_5{-}NH{-}C_6H_4{-}C_6H_4{-}NH{-}C_6H_5$, (*Wieland*, Ber. **39**, 1503) is formed, together with a reddish-violet substance, which is apparently a quinoid addition product of sulfuric acid and tetraphenylhydrazine (*Wieland,* Ber. **40,** 4263). The reddish violet color of the solution soon changes, however, to a deep blue. The blue compound is the same as that produced by the action of nitric acid (and other oxidizing agents) on diphenylamine, *viz., prim*-**diphenylbiphenoquinonediimonium sulfate,** $[C_6H_5{-}N{=}C_6H_4{=}C_6H_4{-}NH{-}C_6H_5]O{-}SO_3H$. Its formation from tetraphenylhydrazine probably takes place through diphenylhydroxylamine (see above) (*Wieland,* Ber. **46,** 3304, 3310). The supposition that the blue color given by diphenylamine with oxidizing agents is due to the intermediate formation of tetraphenylhydrazine seems to be unfounded (*Wieland,* Ber. **46,** 3296).

6. **Oxygen** has no action on the diaryl nitrogens.

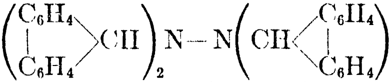
TETRAARYLHYDRAZINES. Tetraphenylhydrazine, colorless, m.p. 144°, dissociation begins at 90° (*Wieland,* Ber. **39,** 1500; Ann. **381,** 200). *sym*-**Diphenyldi-*p*-tolylhydrazine,** m.p. 123°. **Tetra-*p*-tolylhydrazine,** m.p. 136°. **Tetra-*o*-tolylhydrazine,** m.p. 112° (not sharp); the yellowish color of its warm solution in benzene is reversible on cooling (*Wieland,* Ann. **392,** 130, 176). **Tetrabiphenylylhydrazine,** m.p. 130° (turning brown). **Tetraanisylhydrazine,** m.p. 90.5°, is colorless in the solid state, yellowish green in benzene, red in nitrobenzene, and colorless in ether. This illustrates the effect of the solvent on the dissociation. Solutions in benzene do not obey *Beer's* law. Light strongly catalyzes self-decomposition (*Wieland,* Ann. **401,** 233). **Mono-*p*-nitrotetraphenylhydrazine,** is orange-red, m.p. 145°. *sym*-**Di-*p*-nitrotetraphenylhydrazine,** red crystals, m.p. 168–169°. **Tetra-(*p*-dimethylamino)-tetraphenylhydrazine,** m.p. 74–76° (turning red), is colorless in the solid state, but gives a strong yellow solution in benzene. Degree of dissociation in benzene about 10%, and in nitrobenzene about 21%. Solutions in benzene do not obey *Beer's* law. Spontaneous decomposition of the compound gives rise to diarylamine, perazine, and the cherry-red **trimethylindamine,** $H_3C{-}N{=}C_6H_4{=}N{-}C_6H_4{-}N(CH_3)_2$ (*Wieland,* Ber. **53,** 1317). In contrast to the above described tetraarylhydrazines, this strongly basic hydrazine forms colorless, normal salts, with a strong N—N linking, with acids (*Wieland,* Ber. **48,** 1082). Tetra-(*p*-dimethylamino)-tetraphenylhydrazine is very sensitive to water (*Wieland,* Ber. **48,** 1078). For other basic tetraarylhydrazines, see *Wieland,* Ber. **53,** 1313. *sym-p,p'*-**Di(acetylamino)tetraphenylhydrazine,** m.p. 124°, turning dark on melting, does not tend greatly to dissociate. *sym-p,p'-Bis*-**(diethylamino)-tetraphenylhydrazine,** m.p. 104° (turning dark); degree of dissociation similar to that of tetraanisylhydrazine. *sym-p,p'*-**Dimethoxy-*p'',p'''-bis*-(dimethylamino)tetraphenylhydrazine,** m.p. 93° (turning dark), is very highly dissociated and is sensitive to acids (*Wieland,* Ber. **53,** 1315, 1323).

MIXED AROMATIC DITERTIARY HYDRAZINES (*Wieland,* Ann. **392,** 133; Ber. **53,** 1329). The introduction of alkyl groups in place of the aromatic residue leads, in the case of the hydrazines, as in that of the arylated ethanes, to less dissociation. *sym*-**Dimethyldiphenylhydrazine** (prepared according to method *4*), b.p. 138° (1 mm.) (partial decomp.), is sensitive to acids, and reacts with nitric oxide when heated. *sym*-**Diethyldiphenylhydrazine,** b.p. 141° (1 mm.) (partial decomp.). *asym*-**Dimethyldiphenylhydrazine** (prepared by methylation of *asym*-diphenylhydrazine), m.p. 52°, is even less dissociated than the *sym*-isomeride. **Cyclic analogues of the dialkyldiarylhydrazines** (ditertiary hydrazines of the quinone series, see *Wieland*, Ber. **53,** 1336), *e.g.*:



$$C_6H_4\!\overset{(CH_2)_3}{\overline{\qquad\qquad}}\!N-N\!\overset{(CH_2)_3}{\overline{\qquad\qquad}}\!C_6H_4$$

are prepared according to method *1*. The "quinoline-hydrazines" show even less tendency to dissociate than the dialkyldiarylhydrazines (dissociation and decomposition commence at 213°). The tendency to decompose is therefore decreased by ring closure. The compounds have no basic properties. Acids bring about the same changes as with the tetraarylhydrazines. **N,N′-bis-(Tetrahydro[1,2,3,4]quinolyl),** formula, see above, m.p. 141–142°. **N,N′-***bis*-**(Tetrahydro[1,2,3,4]methyl[6]quinolyl),** m.p. 107–108°. **N,N′-***bis*-**(Tetrahydro[1,2,3,4]methoxy[6]quinolyl),** m.p. 117–118° (turning red).

Tetrafluorenylhydrazine,  $\left(\begin{matrix}C_6H_4\\ |\\ C_6H_4\end{matrix}\!>CH\right)_2N-N\left(CH<\!\begin{matrix}C_6H_4\\ |\\ C_6H_4\end{matrix}\right)$, m.p. 243° (dec.), is prepared by passing oxygen into molten 9-aminofluorene at 70° (*Goldschmidt*, Ann. **456,** 161). Even at ordinary temperature the compound shows a green color due to dissociation. The dissociation increases in the series of solvents: ether, acetone, toluene, benzene, pyridine. There is no dissociation in methyl or ethyl alcohol. Dissociated solutions do not obey *Beer's* law. Difluorenylnitrogen does not react with nitric oxide, though it does with nitrogen dioxide. The hydrazine shows the characteristic sensitivity toward acids.

TETRABENZYLHYDRAZINE. Tetraalkylhydrazines have so far not been prepared (but diethylnitrogen, obtained as an intermediate product in the decomposition of the tetrazene, can be fixed by nitric oxide). Tetrabenzylhydrazine can, however, be prepared (*Wieland*, Ber. **53,** 1330). It is a very stable compound, m.p. 139.5°, b.p. about 260° (32 mm.), when the compound can be partially distilled unchanged. Tetrabenzylhydrazine dissolves in concentrated sulfuric acid without decomposition, but simply forming a salt. If, however, the substance is heated with concentrated sulfuric acid to a high temperature, the benzyl groups break away:

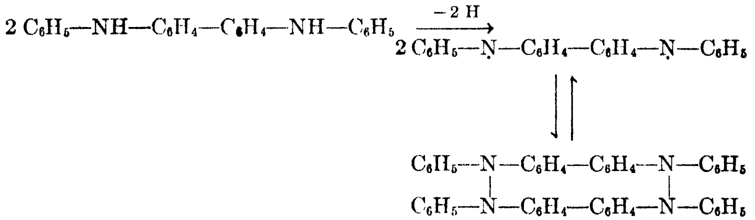
$$(C_6H_5-CH_2)_2\,N-N\,(CH_2-C_6H_5)_2 + 4\,HCl \rightleftarrows 4\,C_6H_5-CH_2-Cl + H_2N-NH_2$$

Even boiling with zinc dust and glacial acetic acid for a day does nothing more than reduce tetrabenzylhydrazine.

DIRADICALS OF THE DIARYLNITROGEN TYPE. These compounds provide particularly good examples of tautomerism. When N,N′-dimethylbenzidine is dehydrogenated, monomolecular, orange-red N,N′-dimethylbiphenoquinonediimine (*Wieland*, Ber. **55,** 1804) is formed.

$$CH_3NH—C_6H_4—C_6H_4—NH—CH_3 \xrightarrow{-2\,H} CH_3—N{=}C_6H_4{=}C_6H_4{=}N—CH_3$$

If N,N′-diphenylbenzidine is submitted to dehydrogenation (with permanganate), a colorless, amorphous compound is formed with the composition of a diimine, but of twice the molecular weight. This substance is colored brown, reversibly, in boiling xylene (*Wieland,* Ber. **55,** 1804). It is a double hydrazine which, on warming, dissociates into a diradical of the diarylnitrogen type. The following processes are therefore occurring:



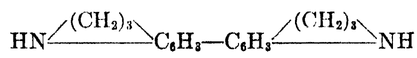
$$2\,C_6H_5—NH—C_6H_4—C_6H_4—NH—C_6H_5 \xrightarrow{-2\,H} 2\,C_6H_5—\underset{\cdot}{N}—C_6H_4—C_6H_4—\underset{\cdot}{N}—C_6H_5 \rightleftarrows \begin{array}{c} C_6H_5—N—C_6H_4—C_6H_4—N—C_6H_5\\ |\qquad\qquad\qquad\qquad| \\ C_6H_5—N—C_6H_4—C_6H_4—N—C_6H_5\end{array}$$

As in the case of the quinonedimethides, these phenomena can be explained from the point of view of tautomerism as follows:

$$R—N{=}C_6H_4{=}C_6H_4{=}N—R \rightleftarrows R—\underset{\cdot}{N}—C_6H_4—C_6H_4—\underset{\cdot}{N}—R$$

When R = alkyl, the equilibrium is displaced toward the left; when it is an aryl group, it is displaced toward the right.

The double radical can be reduced to the diarylbenzidine. They add on nitric oxide, giving *bis*-nitrosamines. They break down at high temperatures in the usual manner, and behave in general like the diaryl nitrogens (the addition of nitric oxide also occurs, however, with the quinonediimines (*Wieland,* Ber. **55,** 1806)). For the N,N′-diarylbenzidines so far investigated, the effect of aryl groups on the dissociation increases in the following order: *p*-chlorophenyl, phenyl, *p*-tolyl, anisyl. It is noteworthy that a cyclic analogue of N,N′-dialkylbenzidine, the quinoline derivative ("quinobenzidine"):



$$HN\overset{(CH_2)_3}{\rule{4em}{0.4pt}}C_6H_3—C_6H_3\overset{(CH_2)_3}{\rule{4em}{0.4pt}}NH$$

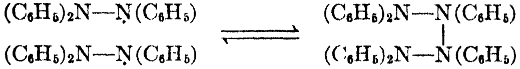
does not give a quinonediimine on dehydrogenation, but a hydrazine. The closure of the hydrogenated ring, appears, therefore, to hinder the biphenyl skeleton from becoming quinoid in structure (*Wieland,* Ber. **55,** 1807).

bis-**Diphenyldibiphenylenehydrazine,** formula above, shows a blue fluorescence in solution. *bis*-**Di-*p*-tolyldibiphenylenehydrazine,** m.p. 205° (indefinite). *bis*-**Di-*p*-chlorophenyldibiphenylenehydrazine,** m.p. 230° (indefinite). *bis*-**Di-*p*-anisyldibiphenylenehydrazine,** m.p. 200° (indefinite); breaks down into radicals in solution even at ordinary temperature. The color of the solution is green (in benzene). **Hydrazine from "quinobenzidine,"** $C_{72}H_{72}N_8$, m.p. 172° (red coloration), is obtained by dehydrogenation of the above-mentioned quinoline derivative, and breaks down into radicals in boiling ethyl benzoate (b.p. 213°) (*Wieland,* Ber. **55,** 1807, 1814).

(b) Triarylhydrazyls and Analogues

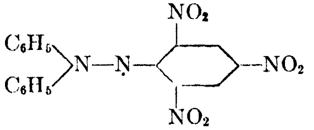
Literature: *Goldschmidt,* Ber. **53,** 44; **55,** 616, 628; Ann. **437,** 104; **473,** 137.

Triphenylhydrazyl, $(C_6H_5)_2N\text{—}N(C_6H_5)$, bears the same relationship to pentaphenylethyl as diphenylnitrogen does to triphenylmethyl. Corresponding to this analogy, the triarylhydrazyls show considerably less tendency to associate than the diarylnitrogens, and also less than the carbon isologues. In contrast to the monomeric pentaphenylethyl, triphenylhydrazyl is in equilibrium with the dimeric hexaphenyltetrazane at room temperature, the radical form strongly predominating (the *"Goldschmidt-Schlenk* principle," Ber. **58,** 418):



$$\begin{matrix}(C_6H_5)_2N\text{—}\dot{N}(C_6H_5)\\(C_6H_5)_2N\text{—}\dot{N}(C_6H_5)\end{matrix} \rightleftharpoons \begin{matrix}(C_6H_5)_2N\text{—}N(C_6H_5)\\ |\\(C_6H_5)_2N\text{—}N(C_6H_5)\end{matrix}$$

Some of the hydrazyls are known only in the monomeric form, *e.g.*, α,α-diphenyl-β-trinitrophenylhydrazyl:



It is rather remarkable that this radical should occur only in the monomeric form, because the introduction of nitro groups into the benzene nucleus of the diarylnitrogens increases their tendency to associate very considerably (the same holds, rather surprisingly, for the introduction of nitro groups into the α-benzene nuclei of the triarylhydrazyls: *Goldschmidt,* Ann. **473,** 148). There is thus a considerable difference in the effect of substituents on the degree of dissociation of diaryl nitrogens and triarylhydrazyls, although these compounds agree on the whole in their properties and chemical reactions.

Acyldiarylhydrazyls have also been prepared. They tend more to associate than the triarylhydrazyls, and, in fact, in this respect α-acyldiarylhydrazyls exceed the β-compounds in the tendency to dimerize.

Some remarkable monomeric carbonic acid derivatives of the hydrazyl type have also been prepared (*Goldschmidt,* Ann. **437,** 204). They are called mono-N-dehydrocarbohydrazides (or, according to the less satisfactory nomenclature of the original, mono-N-dehydrocarbazides), and are formulated as $RR'N\text{—}\dot{N}\text{—}CO\text{—}NH\text{—}NRR'$ (where $R = R' = C_6H_5$, or $R = C_6H_5$, $R' = CH_3$).

1. *Triarylhydrazyls*

METHODS OF FORMATION. *1.* The triarylhydrazyls are prepared by the oxidation of triarylhydrazines (with lead dioxide at −60° in methyl ether solution). The reaction is analogous to that used in the preparation of the diarylnitrogens):

$$\underset{\displaystyle\mathrm{H}}{\mathrm{Ar_2N{-}\overset{}{N}Ar}} \xrightarrow{-\mathrm{H}} \mathrm{Ar_2N{-}\underset{\cdot}{N}Ar}$$

To separate the product, the methyl ether is separated in a vacuum at −70°. For technique, see *Goldschmidt*, Ber. **53,** 54.

2. The transformation of triphenylhydrazine into triphenylhydrazyl by irradiation (which also brings about decomposition) is of theoretical interest. See *Goldschmidt*, Ber. **53,** 48. See method *6* for the triarylmethyls, p. 394.

PROPERTIES. Hexaphenyltetrazane is almost white at −80°, but becomes colored green on warming. Its solutions are pale greenish blue at −80°, and take on the deep blue color of triphenylhydrazyl on warming. The solutions do not obey *Beer's* law.

CHEMICAL PROPERTIES. *1.* **Spontaneous decomposition.** The triarylhydrazyls are very unstable. At room temperature the deep blue color of triphenylhydrazyl solutions changes from green to reddish brown. Diphenylamine and quinonearildiphenylhydrazone, $(C_6H_5)_2N{-}N{=}C_6H_4{=}N{-}C_6H_5$, are among the products of decomposition.

2. **Nitric oxide** combines with triarylhydrazyls to give unstable addition compounds, $Ar_2N{-}N(Ar){-}NO$ (in the same way as it does with the diarylnitrogens).

3. **Triphenylmethyl** reacts with triarylhydrazyls (like the diarylnitrogens). The addition products have not been isolated (see *Goldschmidt*, Ber. **53,** 46).

4. **Hydroquinone** converts almost all the hydrazyls quantitatively into hydrazines:

$$2\,Ar_2N{-}\underset{\cdot}{N}Ar + C_6H_4(OH)_2 \rightleftharpoons 2\,Ar_2N{-}N(H)Ar + O{=}C_6H_4{=}O$$

5. **Hydrazobenzene** reacts even more readily with the hydrazyls:

$$2\,ArN{-}\underset{\cdot}{N}Ar + C_6H_5NH{-}NHC_6H_5 \rightleftharpoons 2\,Ar_2N{-}N(H)Ar + C_6H_5N{=}NC_6H_5$$

6. **Acids** react very readily with the hydrazyls (*Goldschmidt*, Ber. **53,** 62).

7. **Oxygen** does not attack the hydrazyls.

Up to the present, three members of this class of compounds have been prepared. In addition to **triphenylhydrazyl** mentioned above, there is the very similar **α,α-diphenyl-β-p-chlorophenylhydrazyl,** $(C_6H_5)_2N{-}\underset{\cdot}{N}{-}C_6H_4{-}Cl$, which is distinguished from the halogen-free compound only by its greater stability and higher degree of dissociation. It is completely monomolecular, even at −20° in solution. Above this temperature, the solution obeys *Beer's* law, but not below it (*Goldschmidt*, Ann. **437,** 195). The above-mentioned **α,α-diphenyl-β-trinitrophenylhydrazyl,** of which the formula is given above, exists only in the monomeric form, and differs from the above-mentioned hydrazyls in color. It resembles potassium permanganate in appearance, both in the solid form and in solution. In contrast to most other compounds of divalent nitrogen, it does not react with nitric oxide.

2. *Diarylacylhydrazyls*

PREPARATION. These compounds are obtained by dehydrogenation of the corresponding hydrazines, the oxidizing agent being potassium ferricyanide, which is rather better than lead dioxide (*Goldschmidt*, Ann. **437,** 199).

PROPERTIES. These radicals usually show a high tendency to associate, and are colored at high temperatures (or concentrations). The compounds acylated in the α-position, $Ar(Ac)N-\dot{N}Ar$, are green; the β-acylated radicals, $Ar_2N-\dot{N}Ac$, are red.

CHEMICAL PROPERTIES. The diarylacylhydrazyls resemble the triarylhydrazyls in their reactions. It is only necessary to mention the characteristic transformation which diphenylacetylhydrazyl and the dimeric tetrazane undergo when HCl is passed into their benzene solutions. *p*-Chloroazobenzene and acetanilide are formed.

DISSOCIATION. *Goldschmidt* used the diarylacylhydrazyls and the corresponding tetrazanes to solve fundamental problems of the chemistry of radicals. These radicals are specially suitable for the purpose, since they react spontaneously and quantitatively with hydroquinone, and hydrazobenzene, and also, the decomposition of the tetrazane is a time reaction. It is therefore possible to follow the position of the equilibrium very accurately by titration, when, by proper choice of the temperature (−18°) and by working in very dilute solutions, the reverse reaction is very considerably slowed down (*Goldschmidt*, Ann. **437,** 200). The accuracy of the method is still further increased by freezing the equilibrium by cooling to −80° (*Goldschmidt*, Ann. **473,** 141). The principal results of these experiments are as follows: *1.* Experiments with diphenyl-β-benzoylhydrazyl show that the degree of dissociation corresponds to *Ostwald's* dilution law. *2.* The use of different solvents shows that the degree of dissociation depends to a large extent on the solvent (increasing solubility of tetrazane corresponds to increasing degree of dissociation). *3.* The values of the dissociation constants obtained make it possible to draw conclusions on the effect of constitution on dissociation, but no simple connection exists. Determinations with diaryl-α-acylhydrazyls (with various acid radicals on the α-N-atom) show that the extent of dissociation to the radical is not connected with the electrolytic dissociation of the acid. *4.* The heats of dissociation of the tetrazanes have been determined from the temperature coefficient of the equilibrium. The energy of dissociation is widely affected by the solvent (see *Goldschmidt*, Ann. **473,** 146, and p. 389.

DIARYL-α-ACYLHYDRAZYLS, $Ac-N(Ar)-\dot{N}-Ar$ (and tetraaryl-α,α'-diacyltetrazanes). The table (see p. 442) gives the properties of these compounds. They are colorless in the solid state, and are not very much dissociated in solution. They are arranged in increasing order of dissociation. **Di-*m*-dimethylaminophenyl-α-acetylhydrazyl,** which shows very little tendency to associate, has only been obtained in solution.

DIARYL-β-ACYLHYDRAZYLS, $Ar_2N-\dot{N}-Ac$ (and tetraaryl-β,β'-diacyltetrazanes). Colorless **tetraphenyl-β,β'-diacetyltetrazane,** m.p. 141° (decomp.), dissolves with a pink color in hot chloro-

α-Acyl	α-Aryl	β-Aryl	M.p. (dec.)	Dissociation color
Cl_2CHCO	C_6H_5	C_6H_5	102-104°	....
$ClCH_2CO$	C_6H_5	C_6H_5	111-112°	....
CH_3CH_2CO	C_6H_5	C_6H_5	117°	....
CH_3CO	C_6H_5	C_6H_5	126°	Brownish violet
C_6H_5CO	C_6H_5	C_6H_5	114°	Green
CH_3CO	p-$CH_3C_6H_4$	p-$CH_3C_6H_4$	109°	Brownish violet
C_6H_5CO	p-$CH_3C_6H_4$	p-$CH_3C_6H_4$	115°	Green

form. As far as degree of dissociation is concerned it lies between the isomeric α-acetyl derivative and the analogous α-benzoyl compound. Colorless **tetraphenyl-β,β'-dibenzoyltetrazane** is strongly dissociated in its blood-red solutions. The accompanying tables give the dissociation characteristics of these compounds and their derivatives substituted in the acyl radical:

Dissociation of some tetraphenyl-β,β'-diacyltetrazanes (Ann. **437**, 201)
Solvent, toluene. Temp., −18°

Both acyls	Per cent radical (dilution 300)	Equilibrium const., $K \times 10^{-7}$	Dissociation const. of acid at 25° $\times 10^{-6}$
C_6H_5CO	24	2,000	66
p-$CH_3OC_6H_4CO$	30	4,300	32
o-$NO_2C_6H_4CO$	4	45	6,500
m-$NO_2C_6H_4CO$	50	23,000	350
p-$NO_2C_6H_4CO$	39	5,300	400

Dissociation of some *sym*-tetraaryl-β,β'-dibenzoyltetrazanes
(Ann. **473**, 142, 146)

α-Aryls		Solvent	Temp.	Equilibrium const., $K \times 10^{-7}$	Heat of dissociation of N—N linkage, kcal.
p-$NO_2C_6H_4$	p-$NO_2C_6H_4$	$CHCl_3$	0°	6	..
p-$NO_2C_6H_4$	C_6H_5	$CHCl_3$	−18.5°	830	18.1
p-BrC_6H_4	p-BrC_6H_4	$CH_3C_6H_5$	−18.6°	145	12.5
p-BrC_6H_4	C_6H_5	$CH_3C_6H_5$	−18.5°	330	9.9
C_6H_5	C_6H_5	$CH_3C_6H_5$	−18.1°	1,150	10.2
p-$CH_3C_6H_4$	C_6H_5	$CH_3C_6H_5$	−18.5°	4,300	8.9
p-$CH_3C_6H_4$	p-$CH_3C_6H_4$	$CH_3C_6H_5$	−18.5°	17,000	8.2
p-$CH_3OC_6H_4$	C_6H_5	$(CH_3)_2CO$	−18.6°	35,000	7.6
p-$CH_3OC_6H_4$	p-$CH_3OC_6H_4$	$(CH_3)_2CO$	0° to −50°	Completely dissociated	..

3. *Mono*-N-*dehydrocarbohydrazides*

These radicals are obtained (like the other hydrazyls) by dehydrogenation of terminally substituted carbohydrazides by lead dioxide at −25° (*Goldschmidt*, Ann. **437**, 204), *e.g.*:

$$(C_6H_5)_2N\text{—}NH\text{—}CO\text{—}NH\text{—}N(C_6H_5)_2 \xrightarrow{-H} (C_6H_5)_2N\text{—}\underset{\cdot}{N}\text{—}CO\text{—}NH\text{—}N(C_6H_5)_2$$

In addition to the radical chosen as an example, the compound $CH_3(C_6H_5)N\text{—}\underset{\cdot}{N}\text{—}CO\text{—}NH\text{—}N(C_6H_5)(CH_3)$ has also been prepared. Both hydrazyls are monomeric in solution. The color of the first, when dissociated, is deep blue, and of the latter, lavender-blue. They react smoothly with triphenylmethyl and hydroquinone, but with difficulty with nitric oxide.

(c) Dithioaryl nitrogens

Dithioarylnitrogens are obtained, according to *Lecher* (Ber. 58, 423), by dehydrogenation of the imides of aromatic sulfenic acids. They exist in equilibrium with the dimeric **tetrathioarylhydrazines,** *e.g.*:

$$2\,(C_6H_5{-}S)_2NH \xrightarrow{-2\,H} 2\,(C_6H_5{-}S)_2\underset{\cdot}{N} \rightleftharpoons (C_6H_5{-}S)_2N{-}N(S{-}C_6H_5)_2$$

To carry out the dehydrogenation the solution of the imide is treated with lead dioxide (which actually readily reacts with the radical) and potassium carbonate (which stabilizes the radical, which is sensitive to acids). In addition to benzenesulfenimide, *o*-nitrobenzenesulfenimide can be dehydrogenated in the same way. The violet solutions of the reaction products do not obey *Beer's* law, and react with nitric oxide, triphenylmethyl, hydroquinone, and hydrazobenzene. The anilide of *p*-toluene-sulfenic acid, $CH_3{-}C_6H_4{-}S{-}NHC_6H_5$, has also been dehydrogenated. The product is red in solution, and apparently contains thio-*p*-tolylphenylnitrogen.

VI. ORGANIC RADICALS WITH MONOVALENT NITROGEN

Radicals with monovalent nitrogen are, without doubt, very short-lived. It has often been assumed that they are intermediate products in reactions, *e.g.*, erroneously in the thermal decomposition of hydrazobenzene (*Goldschmidt*, Ber. 55, 3217). On the other hand, it can be proved (*Wieland*, Ber. 48, 1112) that triphenylhydrazine decomposes in boiling xylene according to the equation:

$$(C_6H_5)_2N{-}NH(C_6H_5) \rightleftharpoons (C_6H_5)_2NH + {:}N{-}C_6H_5$$

Instead of obtaining phenylnitrogen, as might be expected, its dimer, azobenzene, is formed. Strong evidence for this view is given by the detection as a product of side-reactions of quinoneanil-diphenylhydrazone, as shown in the following equations:

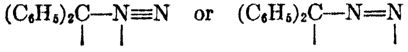
$$C_6H_5{-}N{:} + H{-}C_6H_4{-}NH{-}N(C_6H_5)_2 \rightleftharpoons C_6H_5{-}NH{-}C_6H_4{-}NH{-}N(C_6H_5)_2 \qquad (a)$$

$$C_6H_5{-}NH{-}C_6H_4{-}NH{-}N(C_6H_5)_2 + C_6H_5{-}NH{-}N(C_6H_5)_2 \longrightarrow C_6H_5N{=}C_6H_4{=}N{-}N(C_6H_5)_2 + C_6H_5NH_2 + NH(C_6H_5)_2 \qquad (b)$$

Actually aniline is also among the reaction products of the thermal decomposition of triphenylhydrazine.

VII. DIRADICALS WITH TRIVALENT CARBON AND TETRAVALENT OR DIVALENT NITROGEN

Diphenyldiazomethane appears to be a diradical of this type. *Schönberg* gives the compound the following formula:



$$(C_6H_5)_2\underset{|}{C}{-}\underset{|}{N}{\equiv}N \quad \text{or} \quad (C_6H_5)_2\underset{|}{C}{-}N{=}\underset{|}{N}$$

See, on the other hand, *Müller*, N. **22**, 335; Z.Elektrochem. **40**, 542; Ann. **517**, 147.

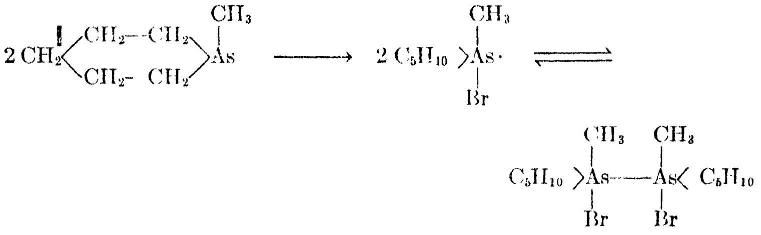
VIII. RADICALS OF OTHER ELEMENTS OF THE FIFTH VERTICAL SERIES OF THE PERIODIC SYSTEM

(a) Phosphorus

When tetraethylphosphonium iodide in liquid ammonia is electrolyzed, the blue solution round the cathode, which is found when tetraethylammonium iodide is electrolyzed, is not observed, but when dimethylpyrone is added, a stable yellow coloration is formed. This has been explained as due to ketyl formation of **tetraethylphosphonium** (*Schlubach*, Ber. **56**, 1894; see tetraalkylammonium radicals, p. 427).

(b) Arsenic

When tetraethylarsonium iodide in liquid ammonia is electrolyzed, the same result is obtained as for the corresponding phosphorus compound (see above). No blue solution is obtained, but a yellow color with dimethylpyrone (*Schlubach*, Ber. **56**, 1894). *Zappi* (Bull. [4], **49**, 366) has obtained a compound of tetravalent arsenic by the careful bromination of methylarsepidine (bromomethylarsepidyl):



The dimer forms colorless crystals, which dissolve at high temperatures giving a yellow solution. The solution reacts with bromine and atmospheric oxygen with formation of:

$$C_5H_{10}{>}As(CH_3)Br_2 \qquad \text{or} \qquad C_5H_{10}{>}As(CH_3)Br{-}O{-}O{-}Br(CH_3)As{<}C_5H_{10}$$

There seem to be no analogous radicals to this.

The existence of compounds of divalent arsenic has not yet been proved. The behavior of the tetraarylhydrazines leads to the assumption that the aromatic analogue of cacodyl would undergo radical dissociation at higher temperatures:

$$Ar_2As{-}AsAr_2 \rightleftharpoons 2\,Ar_2As$$

The same conclusion is arrived at from the fact that the central bond of **tetraphenylcacodyl** is attacked by oxygen. It has, however, been shown that this compound is not markedly dissociated into radicals in boiling benzene (*Schlenk*, Ann. **394**, 216). Work with other **tetraaryldiarsyls** has also led to no positive result (*Blicke*, Am. **52**, 780).

(c) Antimony

"**Antimony cacodyl**" (m.p. 17.5°) and **tetraethyldistibyl** (m.p. −61°) show no tendency to break down into radicals, but, as would be expected, rather the reverse. In the solid state, the first compound is deep red, and the latter yellow. When fused, both compounds form yellowish liquids (*Paneth*, Trans.Faraday Soc.

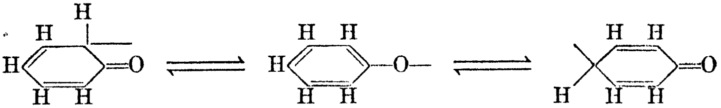
30, 179). The central link of **tetraaryldistibylene** is acted upon by oxygen and by iodine, but no dissociation into radicals has been observed (*Blicke*, Am. **55**, 1198).

IX. ORGANIC RADICALS WITH MONOVALENT OXYGEN

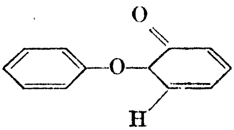
The intermediate formation of organic radicals with monovalent oxygen was first proved by *Wieland* (Ber. **44**, 2550) in the thermal decomposition of triphenylmethyl peroxide into benzpinacone diphenyl ether (p. 422). In the later cases of the formation of radicals with monovalent oxygen it is a matter rather of the equilibrium between peroxides and the hemimers produced by breaking the O—O bond. In the same way as for the most important classes of compounds with trivalent carbon and divalent nitrogen, the loading of the linkage with aromatic radicals leads to its rupture. The organic radicals with monovalent oxygen are the aroxyls, which are in equilibrium with the diaryl peroxides:

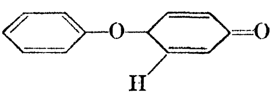
$$\text{Ar—O—} + \text{—O—Ar} = \text{Ar—O—O—Ar}$$

From the dissociation process it can be concluded that these radicals will not be affected by oxygen. There are also cases of equilibrium between the aroxyls and the tautomeric radicals with trivalent carbon (α- and γ-ketomethylenes):



The assumption of this tautomeric equilibrium leads to the further conclusion that there are many possibilities of association, as, in addition to peroxides and three ethane forms, *o*- and *p*-quinol ethers can be produced by combination of aroxyl with the two ketomethyl forms:





In order to study the properties of compounds with monovalent oxygen it is most convenient to take the aroxyls in which the abovementioned tautomerism is very slight. The **phenanthroxyls,** which will be dealt with first, are very suitable. Then the multinuclear dehydrogenation product of *o*-cresol, which is regarded as an aroxyl, will be dealt with.

DEHYDROPHENOLS will then be described; their reactions indicate the existence of tautomerism between the aroxyl form and the ketomethyl form.

For the intermediate formation of radical peroxides, see *Ziegler*, Ann. **504**, 162.

For the occurrence of "active radicals" in the electrolysis of phenols and carboxylic acids in liquid ammonia, see *Goldschmidt*, Ber. **64**, 1744. It is necessary to have the solution sufficiently acid. There is transport of the solute from cathode to anode, formation of hydrogen (3 vol.) at the cathode, and nitrogen (1 vol.) at the anode. It is assumed that the ion of the acid radical forms a particularly reactive radical after discharge, which decomposes the ammonia. Aroxyls formed by dehydrogenation cannot effect this.

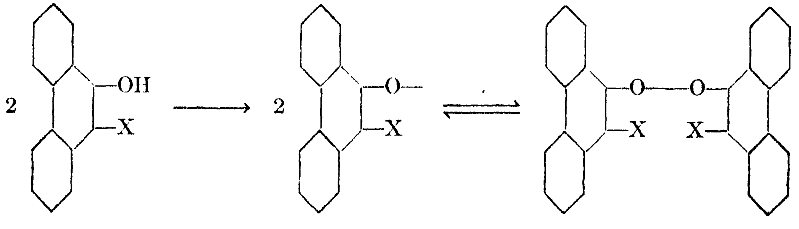
For substances supposed to be aroxyls ("anthoxyls") which were first regarded as compounds of trivalent carbon (oxanthronyls), but which are not radicals, see *Scholl*, Ber. **66**, 514; **67**, 1919, 1922.

At the end of this section, **nitroso compounds** will be discussed. They may be regarded as diradicals with divalent nitrogen and monovalent oxygen.

(a) Phenanthroxyls

Literature, see *Goldschmidt*, Ber. **55**, 3197; Ann. **438**, 202; **445**, 123.

The phenanthroxyls are prepared by dehydrogenation of 10-phenanthrols substituted in the 9-position, by means of potassium ferricyanide (or aqueous alkaline solution) or lead dioxide, X = $-OCH_3$ or $-OC_2H_5$, Cl, Br, *etc.*:



PROPERTIES. The phenanthroxyls differ from all the radicals so far dealt with in the slowness (often several hours) with which equilibrium is attained. The comparatively weak (greenish yellow) color of 9-alkoxy-10-phenanthroxyls (*Goldschmidt*, Ber. **55**, 3205) should also be mentioned.

CHEMICAL PROPERTIES. *1.* **Oxygen** has very little effect on the phenanthroxyls. After many days' action (preferably in the light) 9-ethoxy-10-phenanthroxyl gives phenanthraquinone, and after some weeks, diphenic acid.

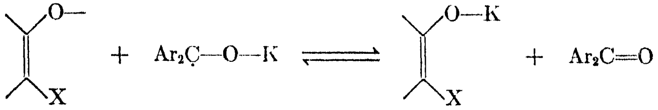
2. **Reducing agents** (*e.g.*, hydriodic acid, hydroquinone, or hydrazobenzene) react, giving phenols ($Ar-O\cdot + H = Ar-OH$). **Hydrazobenzene** reacts quantitatively according to the equation:

$$2\,Ar-O\cdot + C_6H_5-N(H)-N(H)-C_6H_5 \rightleftharpoons 2\,Ar-OH + C_6H_5-N{=}N-C_6H_5$$

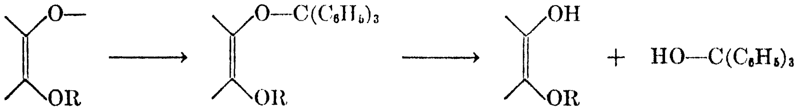
The reaction can be used for the volumetric determination of the equilibrium constant (*Goldschmidt*, Ann. **438**, 204; see p. 441).

3. **Bromine** converts 9-ethoxy-10-phenanthroxyl quantitatively into phenanthraquinone (*Goldschmidt*, Ber. **55,** 3203). For the action of halogens on 9-chloro-10-phenanthroxyl see *Goldschmidt*, Ann. **438,** 207.

4. **Metal ketyls** (p. 415) give up their metal atom to phenanthroxyls:



5. **Triphenylmethyl** forms a noncrystallizable addition product with 9-alkoxy-10-phenanthroxyls. When hydrolyzed it gives triphenylmethanol and 9-alkoxy-10-phenanthrol:



6. **Nitric oxide** does not react with the phenanthroxyls.

PHENANTHROXYLS. 9-**Methoxy- and** 9-**ethoxy-10-phenanthroxyl.** These compounds are colorless in the dimeric form, m.p. (dec.) 165° and 138°, respectively. The color of their solutions is at first bright yellowish green, but deepens on standing (equilibrium is slowly attained in about $2^1/_2$ hours). The color intensity of a freshly prepared solution is only about 0.4 of that of a solution 3 hours old. Degree of dissociation in $N/100$ solution in benzene is about 37% and 62% for the two compounds. 9-**Phenoxy-10-phenanthroxyl** and 9,9′-**diphenoxy-10,10′-diphenanthryl peroxide,** colorless crystals (m.p. 166–167°, dec.). The colorless solutions in chloroform and pyridine become colored pale pink and dark pink, respectively, on boiling, in consequence of dissociation. 9-**Acetoxy-10-phenanthroxyl** and 9,9′-**diacetoxy-10,10′-diphenanthryl peroxide,** colorless crystals, m.p. 208–209° (dec.); solution colorless, no dissociation detected. 9-**Chloro-10-phenanthroxyl;** dimer, colorless crystals, m.p. 124–125° (dec.); monomer, deep bluish red flocks, which dissolve giving a solution of the same color. Degree of dissociation in pyridine (17°, dilution 100), 50%. Dissociation constant in pyridine, 0.005. For the strong effect of solvent and temperature on the velocity and degree of dissociation, see *Goldschmidt*, Ann. **438,** 206. 9-**Bromo-10-phenanthroxyl,** dimer, colorless crystals, m.p. 107–109° (dec.). This compound resembles closely the chloro compound (see above) in properties and degree of dissociation, but differs from it in the much greater ease of decomposition, and by the considerable effect of increase of temperature on the equilibrium constant (*Goldschmidt*, Ann. **445,** 127).

(b) Dehydro-*o*-cresol

Literature: *Pummerer*, Ber. **58,** 1812; *Goldschmidt*, Ber. **55,** 3194; Ann. **478,** 1.

Many simple aromatic compounds with phenolic hydroxyl groups when dehydrogenated give reaction products which are highly colored in solution. The green to bluish green solution obtained in this way from guaiacol behaves as if it contained a radical with monovalent oxygen. The dehydrogenation product of *o*-cresol has been more fully investigated. When a solution of *o*-cresol is shaken with lead dioxide a deep blood-red color is produced. This is due to a radical of monovalent oxygen, but it is a secondary product. It is very likely that the first product is the aroxyl, and this reacts with its tautomeric ketomethyl form. The following formula has been proposed for the blood-red compound:

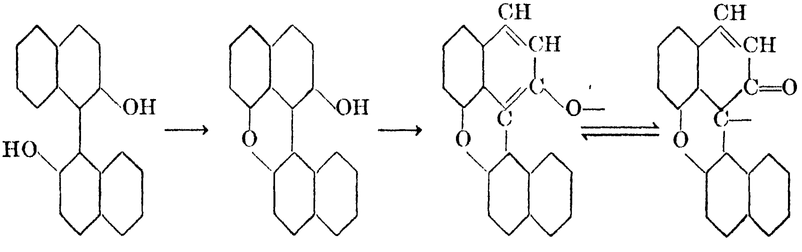
$$CH_3[2]C_6H_4[1]—O—[4']C_6H_3[2']CH_3[1']—O—[4'']C_6H_3[2'']CH_3[1'']—O—$$

(instead of the linkings being in the 4″ and 4′ positions, they could be in the 6″ and 6′ positions.) In solution the radical is 70–90% in the monomeric form. It is very unstable. It is not attacked by atmospheric oxygen, but it reacts almost spontaneously with hydrazobenzene, phenylhydrazine, and triphenylmethyl, being decolorized. For dehydro-*p*-cresol, see p. 450.

(c) Tautomeric Dehydrophenols

Literature: *Pummerer*, Ber. **61**, 1102 and earlier papers; Vol. III of "Naturwissenschaftliche" series of "Wissenschaftliche Forschungsberichte," p. 17; Z. angew.Chem. **38**, 817.

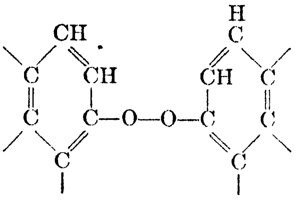
A radical which can exist in the aroxyl form and the tautomeric ketomethyl form is obtained by dehydrogenation of *β*-binaphthol (2,2′-dihydroxy-1,1′-binaphthyl) through the intermediate stage of hydroxybinaphthylene oxide:

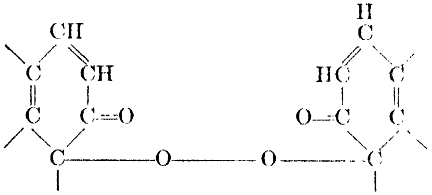


(*Pummerer*, Ber. **52**, 1410). The dimer of the radical is the peroxide (I, p. 449) obtained from association of two aroxyl molecules. On the other hand, the tautomeric ketomethyl can give rise to a peroxide (II, p. 449) by the energetic action of oxygen.

The difference between the aroxyl form and its dimer (I), and the ketomethyl form and its peroxide (II) is that, in regard to its action with permanganate, the former is aromatic in character, whereas the latter has a ring system with a quinone nucleus. The dehydro compounds of a series of phenols, especially *α*-substituted *β*-naphthols, are to be regarded at least partly as quinone ethers. Decomposition into radicals has not been proved in these cases. Their ease of fission with many reagents indicates that the difference is only one of degree (*Pummerer*, Ber. **47**, 2957; **52**, 1392, 1403).

(I)





(II)

PREPARATION of dehydrohydroxybinaphthylene oxide (*Pummerer*, Ber. **59,** 2166). The dehydrogenation is best carried out in dilute ether solution at 0°, with an aqueous alkaline solution of potassium ferricyanide.

PROPERTIES. Dehydrohydroxybinaphthylene oxide forms brownish yellow crystals (color of the dimer), which form a brownish violet solution. Very dilute (completely dissociated) solutions are pure reddish violet. The solutions show an intense blue fluorescence, and a characteristic band spectrum. They are very sensitive to light and mineral acids. The solution in nitrobenzene is not a conductor (*Pummerer*, Ber. **47,** 1472; **59,** 2166).

DISSOCIATION. *Pummerer* has investigated solutions of dehydrohydroxybinaphthylene oxide, and by colorimetric experiments has followed the dissociation of the substance with dilution until completely dissociated. The solvent exerts a marked influence on the degree of dissociation. There is no connection between the dielectric constant of the solvent and the dissociation (Ber. **47,** 1477; **52,** 1418).

CHEMICAL PROPERTIES. *1.* **Spontaneous decomposition.** Dehydrohydroxybinaphthylene oxide and similar dehydrophenols break down according to *Wieland's* rule when their solutions are boiled (Ann. **401,** 234). The first-mentioned compound gives equal quantities of hydroxybinaphthylene oxide and binaphthylene dioxide. The decomposition is considerably accelerated by picric acid, and by light (*Pummerer*, Ber. **47,** 1482, 2962).

In almost all reactions in solution, dehydrohydroxybinaphthylene oxide behaves as an aroxyl. It is only in the reaction with oxygen that the radical reacts as a ketomethyl.

2. **Oxygen** does not have a great effect on dehydrohydroxybinaphthylene oxide, so that it can be prepared without excluding air. When oxygen is passed into it for some time, it forms the peroxide of the ketomethyl form (*Pummerer*, Ber. **47,** 1479).

3. **Potassium permanganate** has no action on a solution of dehydrohydroxybinaphthylene oxide in acetone or pyridine at −30°. At this temperature the dehydrophenol is completely bimolecular, and contains no quinone nuclei. It is then an aromatic peroxide (*Pummerer*, Ber. **59,** 2166). At higher temperatures the dehydrophenol is attacked by permanganate (see p. 449).

4. **Reducing agents** (*e.g.*, hydroquinone) act on the aroxyl forms of the dehydrophenols, re-forming the phenolic hydroxyl group (p. 446; *Pummerer*, Ber. **47,** 1483; **52,** 1409).

5. **Bromine** and other halogens do not act on the dehydrophenols (*Pummerer*, Ber. **47,** 1481, 2961).

6. **Sodium** reacts with dehydrohydroxybinaphthylene oxide forming the sodium salt of hydroxybinaphthylene oxide.

7. **Triphenylmethyl** reacts with the dehydrophenols forming the trityl ethers, according to the equation:

$$\text{Ar—O}\cdot + \cdot\text{C}(\text{C}_6\text{H}_5)_3 \rightleftharpoons \text{Ar—O—C}(\text{C}_6\text{H}_5)_3$$

(For further details, see *Pummerer*, Ber. **47,** 2959; **61,** 1104.)

8. **Nitric oxide** in chloroform does not react markedly with dehydrohydroxybinaphthylene oxide, but in benzene and ether it reacts at once forming a yellow unstable solution (*Pummerer*, Ber. **47,** 1485).

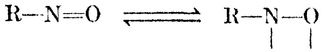
9. **Acids** react very readily with dehydrohydroxybinaphthylene oxide (*Pummerer*, Ber. **47,** 1481; p. 449).

10. **Mutual replacement.** Many dehydrophenols can be prepared by the action of phenols on dehydro-(tetrachloro-*p*-cresol) which has a higher oxidation potential (*Pummerer*, Ber. **52,** 1404; see pp. 400, 416).

DEHYDROPHENOLS. **Dehydrohydroxynaphthalene oxide,** m.p. 144° (or 149°; see *Pummerer*, Ber. **59,** 2166); for further details see above. **Binaphthyl-*bis*-peroxybinaphthylene oxide,** colorless crystals, intermediate product in the conversion of β-binaphthol into dehydrohydroxybinaphthylene oxide (*Pummerer*, Ber. **59,** 2162; **61,** 1102). **Dehydro-2-naphthol** (= 2-hydroxy-1,2′-binaphthyl ether), colorless crystals, m.p. 196° (*Pummerer*, Ber. **52,** 1406, 1414). **Dehydro-1-methyl-2-naphthol,** formerly known as naphthomethylenequinone (2-naphthaquinone 1-methide), yellow crystals, m.p. 133–134° (*Pummerer*, Ber. **47,** 2958; **52,** 1403). **Dehydro-1-bromo-2-naphthol,** regarded as a quinone ether, yellow crystals, m.p. 115–116° (*Pummerer*, Ber. **52,** 1404). **Dehydro derivative of di-(β-hydroxy-α-naphthyl)methane,** $\text{HO}[\beta]\text{C}_{10}\text{H}_6[\alpha]\text{—CH}_2\text{—}[\alpha']\text{C}_{10}\text{H}_6[\beta']\text{OH}$, pale yellow crystals, m.p. 171–172°, regarded as a cyclic quinone ether (*Pummerer*, Ber. **47,** 2958). **Dehydro derivative of di-(β-hydroxy-α-naphthyl)-ethane,** $\text{HO}[\beta]\text{C}_{10}\text{H}_6[\alpha]\text{—CH}_2\text{—CH}_2\text{—}[\alpha']\text{C}_{10}\text{H}_6[\beta']\text{OH}$, yellow crystals, m.p. 143°, regarded as a cyclic quinone ether (*Pummerer*, Ber. **52,** 1392). **Dehydro-(tetrachloro-*p*-cresol),** formerly regarded as tetrachloro-(*p*-methylenequinone), (tetrachloro-*p*-quinonemethide), yellow crystals (*Pummerer*, Ber. **47,** 2964; **52,** 1401, 1404). **Dehydro-*p*-cresol** is a compound with none of the characteristics of a radical (Ber. **58,** 1808).

X. DIRADICALS WITH DIVALENT NITROGEN AND MONOVALENT OXYGEN

The properties of **nitroso compounds** lead to the conclusion that they exist in tautomeric equilibrium as follows:



$$R{-}N{=}O \rightleftharpoons R{-}\underset{|}{N}{-}\underset{|}{O}$$

They can thus be regarded as diradicals with divalent nitrogen and monovalent oxygen (*Walden*, Chem.der fr.Rad., p. 235; *Goldschmidt*, Ann. **442,** 246).

The nitroso compounds (including the pseudonitrols, nitrosites, and nitrosates) have already been dealt with elsewhere. We shall here deal with only those properties and reactions which bear on their radical nature.

PROPERTIES. Many nitroso compounds are colorless and dimeric in the solid form, but in the molten state or in solution they are blue or green, and have a smaller molecular weight (going down to that for the monomer). Heating favors the formation of the monomeric, colored form, cooling, the reverse. As early as 1898, *Piloty* (Ber. **31,** 220, 456) recognized that this was due to a dissociation process. There is, therefore, an equilibrium

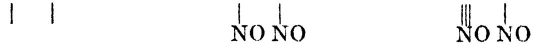
$$(RNO)_2 \rightleftharpoons 2\,RNO$$

By means of suitable substituents (large aromatic radicals) the equilibrium can be displaced so far to the right that the nitroso compounds are colored even in the solid state. There are, therefore, many analogies with the well-known phenomena of radical chemistry. For determinations of molecular weights of nitroso compounds in solution, see *Schmidt*, Ber. **33,** 875; *Bamberger*, Ber. **34,** 3877; *Piloty*, Ber. **35,** 3100, 3114, 3116; *Schmidt*, Ber. **35,** 2323, 2336; *Bamberger*, Ber. **36,** 689.

CHEMICAL PROPERTIES. See *Goldschmidt*, Ann. **442,** 246.

1. **Spontaneous decomposition.** The nitroso compounds break down according to *Wieland's* rule (Ann. **401,** 234). Thus nitrosobenzene (in benzene solution) slowly breaks down into nitrobenzene and azoxybenzene, among other substances. The decomposition is accelerated by light (*Bamberger*, Ber. **35,** 1606).

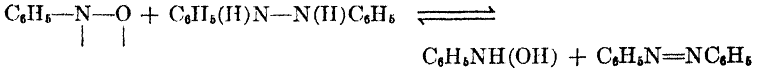
2. **Nitric oxide** converts nitrosoaryls into diazonium nitrates probably according to the equation:



$$Ar{-}\underset{|}{N}{-}\underset{|}{O} \longrightarrow Ar{-}\underset{\substack{|\\NO}}{N}{-}\underset{\substack{|\\NO}}{O} \longrightarrow Ar{-}\underset{\substack{|||\\N}}{N}{-}\underset{\substack{|\\NO}}{O}$$

3. **Triphenylmethyl** reacts in a very complicated manner with nitrosobenzene, though it can be said that addition first takes place (*Goldschmidt*, Ann. **442,** 247).

4. **Hydrazobenzene** from which hydrogen is withdrawn with radicals containing divalent nitrogen and monovalent oxygen, undergoes a completely analogous dehydrogenation with nitrosobenzene:



$$C_6H_5\text{—}\underset{|}{N}\text{—}\underset{|}{O} + C_6H_5(H)N\text{—}N(H)C_6H_5 \rightleftharpoons C_6H_5NH(OH) + C_6H_5N{=}NC_6H_5$$

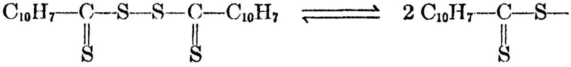
XI. ORGANIC RADICALS WITH TRIVALENT SULFUR

When a solution of triethylsulfonium iodide in liquid ammonia is electrolyzed, there is no blue coloration round the cathode (as in the case of tetraethylammonium iodide), but the addition of dimethylpyrone gives a yellow coloration, and a red substance separates. Azobenzene produces a brown coloration, and tetraphenylethylene a pale pink color. These all indicate that triethylsulfonium exists in the liquid ammonia (*Schlubach*, Ber. **56**, 1894).

XII. ORGANIC RADICALS WITH MONOVALENT SULFUR (THIYLS)

The methods of formation and reactions of the diaryldisulfides have already been dealt with, and it has been pointed out that the binding between the sulfur atoms in these substances must be very loose. *Schönberg* (Ber. **66**, 1932) has found that diphenyl disulfide and *bis*-(thio-α-naphthoyl) disulfide decompose in solution to form radicals with monovalent sulfur (known as phenylthiyl and thio-α-naphthoylthiyl):

$$C_6H_5S\text{—}SC_6H_5 \rightleftharpoons 2\,C_6H_5\text{—}S\text{—}$$



$$C_{10}H_7\text{—}\underset{\underset{S}{\|}}{C}\text{—}S\text{—}S\text{—}\underset{\underset{S}{\|}}{C}\text{—}C_{10}H_7 \rightleftharpoons 2\,C_{10}H_7\text{—}\underset{\underset{S}{\|}}{C}\text{—}S\text{—}$$

PROPERTIES. Diphenyl disulfide is colorless in the solid form, but becomes yellow when melted or dissolved (*Schönberg*, Ber. **48**, 525; **66**, 1940). *Bis*-**(thio-α-naphthoyl) disulfide** is red in both the solid and dissolved states (*Houben*, Ber. **39**, 3230; *Schönberg*, Ber. **65**, 1864; **66**, 1940). Solutions of these compounds do not obey *Beer's* law, and are strongly thermochromic. So far it has not been possible to confirm the existence of the radicals in solution by molecular weight determinations, since at the concentrations used in cryoscopic measurements the dissociation is too small. Solutions of *bis*-(thio-α-naphthoyl) disulfide in naphthalene do not conduct the electric current (at 100°).

For the method of testing *Beer's* law by an improved method due to *Rupp*, see *Schönberg*, Ber. **66**, 1941.

CHEMICAL PROPERTIES. *1.* **Spontaneous decomposition.** Diaryl disulfides break down according to *Wieland's* rule (Ann. **401**, 234) into diaryl monosulfides and diaryl trisulfides (*Hinsberg*, Ber. **43**, 1874).

2. **Triphenylmethyl** adds on to phenylthiyl forming triphenylmethylphenyl sulfide (*Schönberg*, Ber. **66**, 242):

$$(C_6H_5)_3C\cdot + \cdot S{-}C_6H_5 \rightleftharpoons (C_6H_5)_3C{-}S{-}C_6H_5$$

3. **Metal ketyls** give up their metal atom to thiyls (see p. 447):

$$Ar{-}S{-} + Ar_2\underset{\cdot}{C}{-}O{-}Na \rightleftharpoons Ar{-}S{-}Na + Ar_2C{=}O$$

4. **Diphenyldiazomethane** reacts with phenylthiyl in the same way as diazomethane reacts with triphenylmethyl (p. 398):

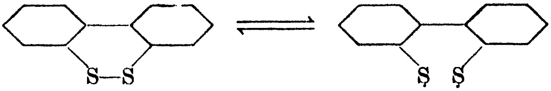
$$2\,C_6H_5{-}S{-} + N_2{=}C(C_6H_5)_2 \rightleftharpoons N_2 + (C_6H_5{-}S)_2C(C_6H_5)_2$$

5. **Heavy metals** (zinc, silver) add on to thio-α-naphthoylthiyl

$$C_{10}H_7{-}C({=}S){-}S{-} + Ag \rightleftharpoons C_{10}H_7{-}C({=}S){-}S{-}Ag$$

6. **Atmospheric oxygen** has no effect on the thiyls.

DIARYL DISULFIDES. Diphenyl disulfide, m.p. 60–62° (Ber. **48**, 525). *Bis*-**(thio-α-naphthoyl) disulfide,** m.p. 169° (*Houben*, Ber. **39**, 3230). *o,o'*-**Biphenylene disulfide,** yellow crystals, m.p. 114.5° (*Schwechter*, Ber. **65**, 1608). The yellow solutions of this compound obey *Beer's* law (*Schönberg*, Ber. **66**, 1934, 1941), which is to be expected, since the formation of the diradical produces no change in the number of molecules, and hence the law of mass action indicates that the position of equilibrium is independent of concentration. This holds for all diradicals in which the change of valence is within the molecule.



XIII. ORGANIC RADICALS WITH TETRAVALENT CHROMIUM

Literature: *Hein*, Ber. 59, 362; **61**, 2255.

When tetraphenylchromium iodide, $(C_6H_5)_4CrI$, is electrolyzed in liquid ammonia, orange-red **tetraphenylchromium,** $(C_6H_5)_4Cr$, separates in the pure state. Since the pentavalence of the chromium in the comparatively stable tetraphenylchromium salt can be regarded: as proved (Ber. **54**, 2708), tetraphenylchromium appears to be a radical with a tetravalent central atom. The compound has been shown to be completely monomolecular when dissolved in pyridine (*Hein*, Ber. **61**, 2257). In the preparation of tetraphenylchromium, the presence of air, light, and moisture must be avoided. Even when kept over concentrated sulfuric acid in a vacuum, the compound undergoes considerable decomposition overnight. In air, tetraphenylchromium immediately becomes tarry, turns dark, and begins to smell of diphenyl. The solution in pyridine is stable in the dark if kept under nitrogen. Water converts tetraphenylchromium into tetraphenylchromium hydroxide (*Hein*, Ber. **59**, 363).

Triphenylchromium, a brownish yellow substance, has been obtained in a similar manner to tetraphenylchromium (*Hein*, Ber. **61,** 2255). Although this compound appears to be completely normal from the point of view of valence, it has the nature of a radical (explanation, *Hein*, Ber. **61,** 2256), and is even more unstable than tetraphenylchromium. Water converts it into triphenylchromium hydroxide.

XIV. ORGANIC RADICALS OF ELEMENTS IN THE THIRD VERTICAL SERIES OF THE PERIODIC SYSTEM

(a) Boron

In comparison with the behavior of the aluminum alkyls (p. 456) it is remarkable that the boron trialkyls show no tendency to associate, while boron hydride, $H_3B—BH_3$, even shows a tendency to dissociate (*Stock*, Ber. **56,** 798). Boron occurs in homopolar compounds in both the trivalent and the tetravalent state, and, on the basis of the composition of hydrofluoboric acid, HBF_4, and its salts, also occurs in the pentavalent state in heteropolar compounds. Diborane, B_2H_6, has been formulated as a heteropolar compound with pentavalent boron (see *Wiberg*, Z.anorg.Chem. **173,** 199; *Stock*, Hydrides of Boron and Silicon, Ithaca, 1933, pp. 158 ff.). Organic compounds of this type are known. They are the complex boron alcoholates, of which the first member, sodium boron ethylate, $Na[B(OC_2H_5)_4]$, was discovered by *Copaux* (C.r. **127,** 719) (see *Meerwein*, Ann. **476,** 113, and *Böeseken*, Koninkl.Akad.Wetenschappen Amsterdam **33,** 23; Rec. **44,** 758). On this basis, heteropolar compounds with tetravalent boron, such as those prepared by *Krause* (Ber. **57,** 216; **59,** 777; **61,** 271; **63,** 934; **64,** 2112)—the compounds of the triphenylboron sodium, $Na[\dot{B}(C_6H_5)_3]$, type—appear to be radicals. Since these compounds conduct the electric current, they are to be regarded as salts, in which the anion has the nature of a radical, as the following comparison shows:

$Na[\underset{\cdot}{B}Ar_3]$	$Na[B(OR)_4]$	$Na[BF_4]$
Triarylboron sodium	**sodium boron alkylate**	**Sodium borofluoride**

Radicals containing tetravalent boron are, therefore, analogous to the aminium salts (p. 431) with the difference that with the latter it is the cation, and not the anion, that has the characteristics of a radical. Triphenylboron sodium resembles very closely triphenylmethyl sodium in its method of formation (from triphenylboron and sodium), and in its properties. This challenges a comparison between triphenylboron and triphenylmethyl (*Krause*, Ber. **57,** 217). In this connection it is of interest to note that the colorless boron triaryls are sensitive to oxygen (*Krause*, Ber. **55,** 1263), and tend to form molecular compounds. They do not tend greatly to associate (*Krause*, Ber. **63,** 2347). Sodium adds on to boron triaryls and boron tribenzyl, but not on to boron trialkyls and boron tricyclohexyl (*Krause,* Ber. **61,** 271; **64,** 2112). Other alkali metals also add on to boron triaryls.

PREPARATION. The combination of boron triaryls with alkali metals is carried out in ether in an atmosphere of nitrogen (for technique, see *Krause,* Ber. **59,** 778).

PROPERTIES. The compounds of the alkali metals with triphenylboron are orange-yellow, though the lithium compound is greenish yellow. Like triphenylmethyl sodium (though to a lesser degree) triphenylboron sodium conducts the electric current in ether solution. It is not affected by light.

CHEMICAL PROPERTIES (*Krause,* Ber. **59,** 777). *1.* **Atmospheric oxygen** reacts very readily with the borontriaryl alkali metals.

2. **Iodine** reacts quantitatively with triphenylboron sodium according to the following equation:

$$2\,(C_6H_5)_3\dot{B}{-}Na + I_2 \rightleftharpoons 2\,(C_6H_5)_3B + 2NaI$$

3. **Mercury** (in excess) acts on triphenylboron sodium with formation of triphenylboron and sodium amalgam. The reaction may, however, be reversed by the use of a concentrated sodium amalgam (about 2.9% Na):

$$(C_6H_5)_3\dot{B}{-}Na + Hg \rightleftharpoons NaHg + (C_6H_5)_3B$$

4. **Triphenylmethyl** withdraws the metal atom from triphenylborylsodium.

5. **Triphenylmethyl chloride** forms triphenylmethyl with triphenylboron sodium, and the triphenylmethyl then reacts with unchanged triphenylboron sodium as in *4* above.

6. **Ethyl bromide** reacts immediately with triphenylboron sodium.

7. **Carbon dioxide** also reacts immediately with triphenylboron sodium.

8. **Ether** combines with the triphenylboron alkali metals in part (in the case of Na and Li) to form the very stable ether compounds, *e.g.,* $(C_6H_5)_3\dot{B}{-}Na,\ (C_2H_5)_2O$. The latter compound loses its ether completely at 180°, the original orange-yellow color becoming pale lemon-yellow (the ether compounds are generally more highly colored than the ether-free compounds). In the formation of triphenylboron sodium the use of ether is not absolutely necessary. It can often be replaced by benzene.

9. **Thermal decomposition.** When triphenylboron cesium is heated to 240–250° in a vacuum, the compound is completely decomposed, benzene being split off (*Krause,* Ber. **59,** 785).

TRIARYLBORYL ALKALI METALS. The compounds of all the alkali metals with triphenylboron have been obtained analytically pure (*Krause,* Ber. **59,** 780 *ff.*). The sodium compounds of **tri-*p*-tolylboron, tri-*p*-xylylboron, tri-α-naphthylboron, tri-*p*-anisylboron,** and **tribenzylboron** have not been obtained in the solid state.

(b) Aluminum

Just as the halides of aluminum (and iron) are classic examples of dissociable compounds, an equilibrium is supposed to exist in the case of the aluminum alkyls:

$$R_3Al—AlR_3 \rightleftharpoons 2\ AlR_3$$

The aluminum alkyls are very sensitive toward atmospheric oxygen (spontaneously inflammable), and hence "it is possible to conclude that trivalent aluminum is unsaturated, and to assume that tetravalent aluminum can exist" (*Walden*, Chem.der fr.Rad., p. 270). For the molecular weight determinations of aluminum methyl and ethyl, which have been carried out by many workers by different methods, see *Quincke*, Ber. **22**, 551; Z.physikal.Chem. **3**, 164. For existence of subsidiary valences in the aluminum triaryls, see *Krause*, Ber. **63**, 2401.

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